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An Experimental Brain Missile Wound; Ascertaining Pathophysiology and Evaluating Treatments to Lower Mortality and Morbidity

Annual Report

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June Davidson

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We evaluated mechanical and chemical regulation of cerebral blood flow (CBF) following a missile wound to the brain in pentobarbital anesthetized cats. Blood flow was measured by microspheres in more than 25 brain areas including brain immediately adjacent to the missile wound track.

After wounding both mechanical and chemical regulation of CBF were greatly impaired. Brain about the missile track was most severely affected. Once ischemic from hemorrhagic hypotension, the wounded brain could not be reperfused despite restoration of mean arterial blood pressure. Brain wounded animals thus exhibited "reperfusion failure"

Following wounding, test animals demonstrated very substantial, but brief, increases in plasma catecholamines.

After brain wounding animals had significant decrements in behavior which gradually recovered up to 30-45 days post-wounding. Some post-wounding defects persisted permanently. We have perfected a model to test drugs to try and improve neurologic recovery after brain wounding.

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SUMMARY

The experiments presented in this report include three areas of investigation: A) the effect of brain wounding on the mechanical and chemical regulation of cerebral blood flow; B) the effect of brain wounding on plasma catecholamines; C) an improved test to measure animal behavior after brain wounding.

A). Mechanical and Chemical Regulation of Cerebral Blood Flow

The experiments included in this study are the first undertaken whereby regional cerebral blood flow (rCBF) and its control after brain wounding have been studied. rCBF was repeatedly measured by microspheres in over 20 brain areas and around the wound track itself in 6 groups of anesthetized, paralyzed cats. Normotensive, wounded cats showed a 29% reduction in whole brain CBFs 45 minutes after wounding. We interpret this as indicating some loss of ability to regulate CBF after brain wounding. Unwounded cats made hypotensive by hemorrhage to a mean arterial blood pressure (MABP) of ~ 40 mmHg showed no change in total CBF; mechanical blood flow regulation (autoregulation) generally remained intact. Ten cats were subject to a brain wound and simultaneous hemorrhagic hypotension. Six cats with higher mean post-wounding intracranial pressure (ICP) and lower mean cerebral perfusion pressure (CPP) had a precipitous drop in rCBF while 4 cats with lower mean ICPs and higher CPPs were able to maintain CBF despite an average MABP reduction to 38 mmHg. In the 4 cats which were able to maintain CBF despite decreasing MABP, restoration of blood pressure resulted in an increased ICP and decreased CBF indicating that the full ability of these brain-wounded cat to autoregulate CBF was impaired. All brain wounded cats subject to hemorrhagic hypotension exhibited reperfusion failure: restoring blood volume did not improve CBF in any.

Normal cats demonstrated a 112% increase in CBF when PCO_2 was increased from 29 to ~ 55 mmHg and a 35% increase when PO_2 was reduced from 127 to ~ 55 mmHg. These normal responses, indicating chemical control of rCBF, were completely abolished throughout the brain following missile wounding. Brain about the wound track was more severely affected.

These data indicate that the missile-wounded brain may completely lose the ability to regulate CBF mechanically or chemically. Hence, neither hemorrhagic hypotension nor hypercapnic hypoxia (hypoventilation) are tolerated by the missile-wounded brain.

B. Plasma Catecholamine Elevations After Brain Wounding

A missile wound to the brain caused immediate elevations in plasma catecholamines suggesting that this response was the result of missile-generated pressure forces acting on the hypothalamus, brain stem, or other brain areas participating in the sympathoadrenal response. Missile wounding causes a rise in intracranial pressure but our experiments showed an ICP increase alone caused a delayed rise in catecholamines not an immediate elevation as was seen with missile wounding.

C. Evaluation of Cat Behavior After Brain Wounding

A improved cat behavior testing paradigm has been developed in which injured animals can be evaluated for recovery of function. This paradigm will be essential for testing drugs which may be able to enhance neurological recovery.

FOREWORD:

In conducting the research described in this report, the investigators adhered to the "Guide for the Care and Use of Laboratory Animals," prepared by the Committee on Care and Use of Laboratory Animals of the Institute of Laboratory Animal Resources, National Research Council (DHEW Publication No. (NIH) 86-23, Revised 1985).

The experiments on mechanical and chemical blood flow regulation in the brain following missile wounding were performed by Dan Torbati Ph.D. and June Davidson, B.Sc.

The plasma catecholamine experiments were performed by Joseph Soblosky, Ph.D. and J. Bryan Farrell, B.Sc.

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Section A

The Effect of Brain Wounding on Mechanical and Chemical Regulation of Cerebral Blood Flow

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REGULATION OF CEREBRAL BLOOD FLOW AFTER A MISSILE WOUND TO THE BRAIN IN ANESTHETIZED CATS

INTRODUCTION

Blood flow to an organ is proportional to blood pressure and inversely proportional to the organ's vascular resistance. Blood flow to any organ is given by the formula:

flow = pressure/resistance

Organ blood vessels are capable of changing their resistance through different mechanisms. Regulation of cerebral blood flow (CBF) is carried out by at least four mechanisms:

1) Mechanical regulation whereby CBF regulatory mechanisms respond to changes in mean arterial blood pressure and/or cerebral perfusion pressure (CPP); (45,47,73,88,106). Mechanical control of flow underlies classical CBF "autoregulation".

2) Chemical regulation in which changes in arterial PO_2 and PCO_2 alter CBF (7,17,46,67,74,99).

3) Metabolic regulation occurs when local CBF changes in response to alterations in local energy metabolism (67,68,139).

4) Neurogenic regulation of CBF may occur by means of sympathetic and cholinergic fibers affecting the larger arterioles of the brain (25,67,102). Autonomic inervation of cerebral blood vessels may come from extracranial sources or from nuclei whose cell bodies originate within the brain itself (CNS), (107).

MECHANICAL BLOOD FLOW REGULATION

The classic example of mechanical blood flow regulation to the brain was demonstrated when blood flow to the brain was shown to be maintained despite a decreasing mean arterial blood pressure (MABP) (106). Brain has an extremely well-developed capacity to maintain its blood flow despite wide changes in MABP. When MABP is reduced, as during hemorrhagic hypotension (HH) or administration of hypotensive drugs, cerebral vasodilation occurs. This decreases the resistance in the cerebral vessels and maintains CBF. If MABP increases to hypertensive levels (i.e. 150 mmHg), cerebral vasoconstriction is induced. The resulting increase in cerebral vascular resistance (CVR) prevents flow from increasing despite the increased MABP. These reactions can hold CBF relatively constant when MABP ranges between 60-150 mmHg, depending on the species. Below and above these blood pressures, CBF autoregulation fails (45,47). Changes in local vascular resistance occur in response to the stretch of vascular smooth muscle (130) or to the accumulation of local metabolites (67,68).

The level of blood pressure in the brain is actually determined by the MABP minus the intracranial pressure (ICP). The difference is the cerebral perfusion pressure (CPP): MABP-ICP=CPP. Since the ICP may change in pathological conditions, the CPP is a better measurement of the pressure of blood perfusing the brain tissue than is the MABP. The lower limit of CBF autoregulation is usually around a CPP of 40 to 60 mmHg (40-43,88,89,142).

CHEMICAL BLOOD FLOW REGULATION

CBF is also regulated chemically by changes in blood PCO_2 and PO_2 (7,57,83,99). Carbon dioxide is a very potent vasodilator of cerebral arterioles. Normally, hypercapnia produces an increase in CBF by decreasing cerebral vascular resistance while hypocapnea causes cerebral vasoconstriction and decreases CBF. Hypoxia leading to severe hypoxemia also results in cerebral vasodilation (7,99) and increased CBF.

CNS TRAUMA AND THE BREAKDOWN OF CBF REGULATION

Mechanical and chemical regulation of blood flow to the brain may be impaired by a variety of insults: intracranial hemorrhage, hypoxia, hypercapnia, ischemia and CNS trauma (7,21,30,65,76,77,89,99,108,114,128). Cerebral blood flow after acute CNS trauma has been studied in experimental animals (10,24,76,77,85,89,108,114,128) and in man (30,110.125). Unlike paradigms of focal brain injury (e.g. cold injury, stab wounds), or those which give only a general concussive effect (various percussion models), brain missile wounding (BMW) creates both focal and generalized brain damage and dysfunction. Therefore, BMW is a unique type of injury. We are unaware of any prior studies which have specifically delineated the effect of a missile wound to the brain upon mechanical or chemical regulation of CBF. Therefore, we sought to determine the extent of mechanical and chemical CBF regulatory dysfunction following a brain missile wound. The questions we asked include: 1) Were mechanical and chemical CBF regulatory mechanisms perturbed mainly around the missile wound track or widely throughout the entire brain; 2) If these regulatory mechanisms were globally disturbed, were some brain areas more disturbed than others?

In our studies, mechanical regulation of CBF (autoregulation) was measured in both unwounded and wounded cats by means of graded hemorrhagic hypotension and subsequent reinfusion of shed blood. Chemical regulation of CBF was tested in normotensive cats by increasing arterial PCO_2 and decreasing arterial PO_2 both before and after BMW. Blood flow was measured by microspheres (11,49,52,79) in up to 24 brain structures and about the missile wound track.

MILITARY SIGNIFICANCE

These experiments, designed to answer the basic physiological questions concerning mechanical and chemical regulation of CBF, simulate the same conditions (i.e. hemorrhagic hypotension, hypercapnea, hypoxia) which the brain-wounded soldier may experience in combat. The results, therefore, are extremely relevant for the mission of the Army Medical Corps because they show how the missile-wounded brain behaves when subjected to a second stress (i.e. HH and respiratory insufficiency leading to hypoxemia). Furthermore, our HH experiments, testing mechanical regulation of blood flow after wounding, were designed to ascertain how the wounded brain reacts to reinfusion of blood. This simulates resuscitation by blood transfusion to a brain-wounded soldier who may also have concomitant HH and shock because of other wounds (e.g. brain wound plus femoral artery wound).

METHODS

SURGICAL PROCEDURES: Our basic surgical procedures have been described in detail in prior reports (Feb 1987; Sept 1987). Briefly, mongrel cats of either sex (2.5 to 5 kg) were deeply anesthetized with 30-40 mg/kg pentobarbital i.p. After endotracheal intubation, one femoral artery was cannulated (PE 160) for blood pressure recording and blood sampling and for measurements of PO_2, PCO_2, pH, blood glucose concentration (BGC), and hematocrit (HCT). In animals used to test mechanical regulation of CBF, the same line was also used to induce hypotension by bleeding and also for blood reinfusion. The second femoral artery was used for placement of an intracardiac PE 90 pigtail catheter for microsphere injection. Catheter tip placement within the left ventricle was determined by pulse pressure recordings and post mortem examination.

Both brachial arteries were cannulated (PE50) to withdraw arterial blood samples for microsphere counting (reference sample method) (52). A femoral vein was also cannulated (PE 90) for additional administration of pentobarbital as needed and gallamine for paralysis. The cat was then placed in a stereotaxic head apparatus, a midline scalp incision was made, and the anterior wall of the right frontal sinus was removed prior to wounding (13).

Three miniature, stainless steel screws connected to shielded wires were used for electroencephalographic (EEG) recording. One screw was placed in the skull over the right parietal cortex and two over the left. A 4 mm diameter left parietal burr hole was made for insertion of a fiberoptic ICP recording probe (Camino, model 420). The EEG screws and the ICP probe were then secured and sealed with methylmethacrylate. Two needle electrodes were placed subcutaneously over the left thoracic cage about 2 or 3 cm anteriolateral to the sternum for electrocardiographic (ECG) recording. After all surgical preparations, the cats were paralyzed with 30-40 mg of i.v. gallamine and immediately placed on a respirator. End expiratory CO_2 was maintained relatively constant by respirator adjustments. The cats were then tested for the effect of wounding upon either mechanical or chemical regulation of CBF.

A: MECHANICAL REGULATION OF CBF TESTED BY HEMORRHAGIC HYPOTENSION

Four groups of cats were used in these experiments:

GROUP I: UNWOUNDED NORMOTENSIVE (7 cats): Cats in this group served as controls. Regional CBFs (rCBFs) were measured 5 times during the 100 min experimental period according to the following schedule:

CBF # 1, control, 10 min before zero time (the time in which wounded animals were injured).

CBFs # 2 to # 5 were measured 5, 20, 45 and 90 min after "zero time". Blood samples (1 ml) for gas and pH analysis, HCT and BGC were taken immediately after each CBF measurement. The five CBF measurements in this group served as controls for the 100 min experimental period.

GROUP II: WOUNDED NORMOTENSIVE (7 cats): Cats in this group received a brain wound by a 2mm, 31 mg steel sphere which traversed the right cerebral hemisphere through the intact cranium (anterior-posterior trajectory). The mean velocity of the wounding spheres was 280 m/s; their mean energy 1.4 Joules (J). Ten minutes prior to wounding a control CBF was measured. CBFs were then measured at 5, 20, 45 and 90 min after brain wounding (zero time). Arterial blood was sampled for blood gases, pH, BGC and HCT at the same times.

GROUP III: UNWOUNDED HEMORRHAGIC HYPOTENSIVE (8 cats): CBFs were first measured in this group when cats were normotensive (MABP 116 ± 5 mmHg) 10 min before bleeding was begun. Starting at "zero time", the MABP was gradually reduced by arterial bleeding to 3 steady-state hypotensive levels: 89 ± 5 mmHg (mild hypotension); 68 ± 4 mmHg (moderate hypotension) and 48 ± 5 mmHg (severe hypotension). These MABP levels were reached 5 min, 20 min, and 45 min after bleeding began. The shed blood was collected in 20 ml heparinized syringes and kept at 37°C until reinfused. After the 4th CBF measurement, at 45 min when the cats were severely hypotensive, the shed blood was reinfused over a 20-30 min period. At 90 minutes, once the MABP had stabilized, the fifth CBF was measured.

GROUP IV: WOUNDED HEMORRHAGIC HYPOTENSIVE (10 cats): Animals in this group were wounded as described for group II and immediately subjected to HH as described in group III. This group specifically examined the effect of a missile wound to the brain upon mechanical regulation of CBF.

B: CHEMICAL REGULATION OF CBF TESTED BY HYPERCAPNIA

For these experiments seven cats were surgically prepared as described above (see SURGICAL PROCEDURES) and five CBF measurements were made in each cat. CBF measurements were performed during normoxic-isocapnia and then after hypercapnia was induced both before and after the cats received a missile wound to the brain. This tested whether the missile-wounded brain responded normally to a hypercapnic challenge. CBFs were measured according to the following scheme:

CBF #1: A control CBF was measured 60 min before the cat received a brain wound when the animal was normoxic-isocapnic.

CBF #2: 10 min after the first CBF the cats were given 5% CO_2 in air to breathe. Exactly 5 min after the start of hypercapnia the second CBF was measured in order to test the normal response to hypercapnia.

CBF #3: After the hypercapnic test, cats were allowed to breathe room air for 40 min. In 3 out of 7 cats, five min before brain wounding, a third CBF measurement was performed following return to normoxic, isocapnic conditions in order to ascertain whether CBFs had returned to control levels after hypercapnia was induced.

CBF #4: 30 minutes following brain wounding an additional CBF measurement was made in all cats when they were normoxic and isocapnic in order to determine the post-BMW baseline for rCBFs.

CBF #5: 45 min following brain wounding the cats were once again made hypercapnic by breathing 5% CO_2 for 5 min, and a final CBF was measured to see whether the wounded brain could respond to a hypercapnic challenge as had the non-wounded brain.

Three cats had only two CBF measurements before BMW (control and hypercapnic trial). These cats had three post-wounding CBF measurements: one 30 minutes after brain wounding (normocapnia); the second 50 minutes after injury (hypercapnia) and the third 90 minutes after injury (normocapnia) to test the ability of CBF in injured brain to recover after a hypercapnic challenge. After BMW 2/7 cats developed CBFs < 10 ml/100 g/min before the hypercapnic challenge. Data from these animals were excluded from final analysis.

C. CHEMICAL REGULATION OF CBF TESTED BY HYPOXIA

Seven cats were subjected to the same surgical and experimental schedules as described for the hypercapnic cats, except these cats were challenged by a 10% O_2 gas mixture to test the CBF response to pre and post-BMW hypoxia. Three cats developed very low CBF after BMW and their CBF data were excluded from final analysis.

MICROSPHERE METHOD FOR BLOOD FLOW MEASUREMENTS:

Radioactive microspheres allow repeated measurements of blood flow in any organ. The microsphere technique is based upon the general equation which indicates:

$$F = Q(t) / (C_i - C_o)$$

where F is the flow in ml/min; Q is the organ tracer (radioisotope) content at the particular time (t); C_i is the amount of the radioactive tracer entering the tissue and C_o is the amount of the tracer leaving the tissue. If C_o equal 0 this formula then becomes:

$$F = \frac{Q(t)}{\int_0^t Ca\ (dt)}$$

where $\int_0^t Ca\ (dt)$ is the integral of the arterial blood concentration of the tracer. To measure blood flow, radiolabelled microspheres are injected into the circulation via a cannula in the left ventricle of the heart. The microspheres mix with the blood and are distributed to organs in proportion to the blood flow at the time of their injection. The integral of the arterial blood concentration may be obtained by withdrawing blood from a systemic artery as the spheres are being injected (mechanical integration of Ca by the reference syringe method). Q(t) is determined by counting the radiolabelled spheres entrapped in the organ of interest.

For measurements of blood flow by microspheres several conditions must be met (11,49,52,79): the spheres must be uniformly admixed with blood issuing from the left ventricle, and C_o must be close to 0. The number of microspheres in the organ sample must be greater than 400 and the reference sample must contain at least 400 microspheres/ml. If these criteria are met, blood flow measurements will have an accuracy with 10% error (11,49).

For our experiments we used 15 μm diameter microspheres labeled with one of five isotopes: 153 Gadolinium (Gd), 113 Tin (Sn), 103 Ruthenium (Ru), 95 Niobium (Nb), and 46 Scandium (Sc). Hence, in each individual animal we could measure 5 CBFs. The different labelled spheres were injected in random order in each experiment. For each blood flow measurement 1.1 to 1.5 million microspheres were injected depending on the weight of the animals. This provided approximately 4000 spheres/gm of brain tissue under normal flow conditions. All tissue and blood samples and microsphere standards were counted in a Gamma Trac Counter. The counting was done at 5 different energy levels which gave optimal isotope peak separation. Each radioassay was corrected for background and overlapping radioactivity from other isotopes (52) by a counting program using an IBM-AT computer which automatically received, processed, and stored counts from the Gamma counter in a computer file. These data were then combined with tissue sample weights which had been obtained by a Mettler electronic balance and also stored in a computer file. All corrected radioisotope data were then expressed as counts/gm of tissue or ml of blood. Radioisotope counts in reference withdrawal syringes from each brachial artery were compared in an attempt to evaluate adequate microsphere mixing with blood. If a counting difference of > 10% existed between the two brachial samples the experiment was rejected.

Computation of blood flow was done by the formula:

Reference blood flow/reference count = tissue flow/tissue counts.

All blood flows in this report are expressed as ml/100g/min.

The microsphere method for measurement of blood flow requires that the spheres do not reach the venous system; i.e. $C_0 = 0$ (49,52). Hence, we used 15 μm diameter microspheres. A-V shunting in the brain was determined in 3 cats (one control normotensive, one wounded, and one hypotensive unwounded) during 5 consecutive measurements by counting microspheres in sagittal sinus blood and comparing sagittal sinus counts to sphere counts in the reference sample.

DISSECTION OF BRAIN AND OTHER ORGANS

At the end of each experiment the cats were euthanized by pentobarbital. The animal was fixed by intracardiac perfusion of 1 liter of saline followed by 1 liter of 10% buffered formaldehyde with the right atrium sectioned to allow egress of blood and fixative from the vascular system. In the studies on mechanical regulation of CBF (groups I to IV) the brain was dissected to 24 anatomical structures according to a previous protocol (126). All frontal, parietal, occipital, and temporal areas as well as thalamus, hippocampus and cerebellum separately were taken from each cerebral hemisphere. Additionally, in wounded cats gray and white matter were taken from a radius of 3 mm about the missile track (periwound tissue). After dissection, individual brain and spinal cord samples were scored in tared vials, re-weighed and then counted. Brain dissection for hypercapnic and hypoxic cats (groups V and VI) was identical, except that corresponding left and right brain structures were counted together. In cats in which pressure regulation of CBF was determined, in addition to the brain and upper cervical

spinal cord the following organs were sampled for determination of organ blood flow (OBF): cardiac muscle, skeletal muscle, spleen, kidney (medulla and cortex separately), lung and adrenal. Tissue samples from these organs were processed as the brain specimens. In cats wherein chemical regulation of CBF was tested only cardiac muscle was taken along with the brain and spinal cord.

All CBF data were correlated with simultaneously determined MABP, ICP and CPP measurements. Total brain CVR was calculated as CPP/total CBF. To demonstrate a linear scale of blood acid-base changes, pH values were also converted to arterial [H+]: pH = - log [H+].

STATISTICAL ANALYSIS

All data are expressed as Mean $\pm$ SE (Standard Error of the Mean). In groups I to IV, where the effect of BMW on mechanical CBF autoregulation was examined, control data were compared with observed changes in various physiological measurements at 5,20,45 and 90 minutes after wounding. All data were evaluated first by ANOVA and then by Dunnett's test (ie repeated measurements over time). In special cases, where indicated, the paired t-test was used to compare control data with post wounding experiments in the same group.

In groups V and VI, the magnitude of the responses to increased pCO_2 or decreased pO_2 before and after wounding were compared. The derived data were first evaluated by ANOVA followed by paired t-tests using the Bonferroni correction for multiple measures.

RESULTS

All data for these experiments are provided in Appendix Tables. Tables I to IV refer to the 4 groups used to evalute mechanical CBF autoregulation. Tables V and VI contain data on chemical CBF regulation, (hypercapnia V and hypoxia VI). Data related to systemic and intracranial pressures as well as blood gases, pH, HCT and BGC are labeled by the letter "A". The rCBF values of all experimental groups are labeled by the letter "B". Organ blood flows are provided in Appendix Tables IC to IVC. Selected data from these tables will be graphically presented to demonstrate the most typical effects of BMW on mechanical and chemical regulation of CBF.

MECHANICAL REGULATION OF CBF

GROUP I, UNWOUNDED NORMOTENSIVE (CONTROL) CATS (N=7): The upper graph of Figure I-A shows the MABP, ICP, and CPP during the 100 min experimental period for control cats. The total CBF (whole brain) and total CVR during 5 consecutive measurements at -10 ("control"), 5, 20, 45 and 90 min are shown in the bargraphs of Fig I-A.

Figure I-B presents selected rCBF values including right and left cortical structures (combined values of frontal, parietal, temporal and occipital cortecies), midbrain and left cerebellar gray matter. These ventilated control cats maintained normoxic, normocapnic blood gas values and pH during 5 CBF measurements (Table I-A). Systemic and intracranial pressures were also maintained within a normotensive range throughout the entire period of experimentation, and no significant changes occurred in either total CBF, CVR or rCBF (Figs I-A & I-B). rCBF values were similar in both hemispheres (Table I-B). Individual (CBF-CPP) relationships for these unwounded normotensive cats are illustrated in Figure I-C, (7 cats x 5 flows). In all cases total CBF remained above 20 ml/100g/min and CPP was greater than 70 mmHg.

A-V (sagittal sinus) microsphere shunting, determined for 5 consecutive CBF measurement in one cat, was less than 0.2 % in each case.

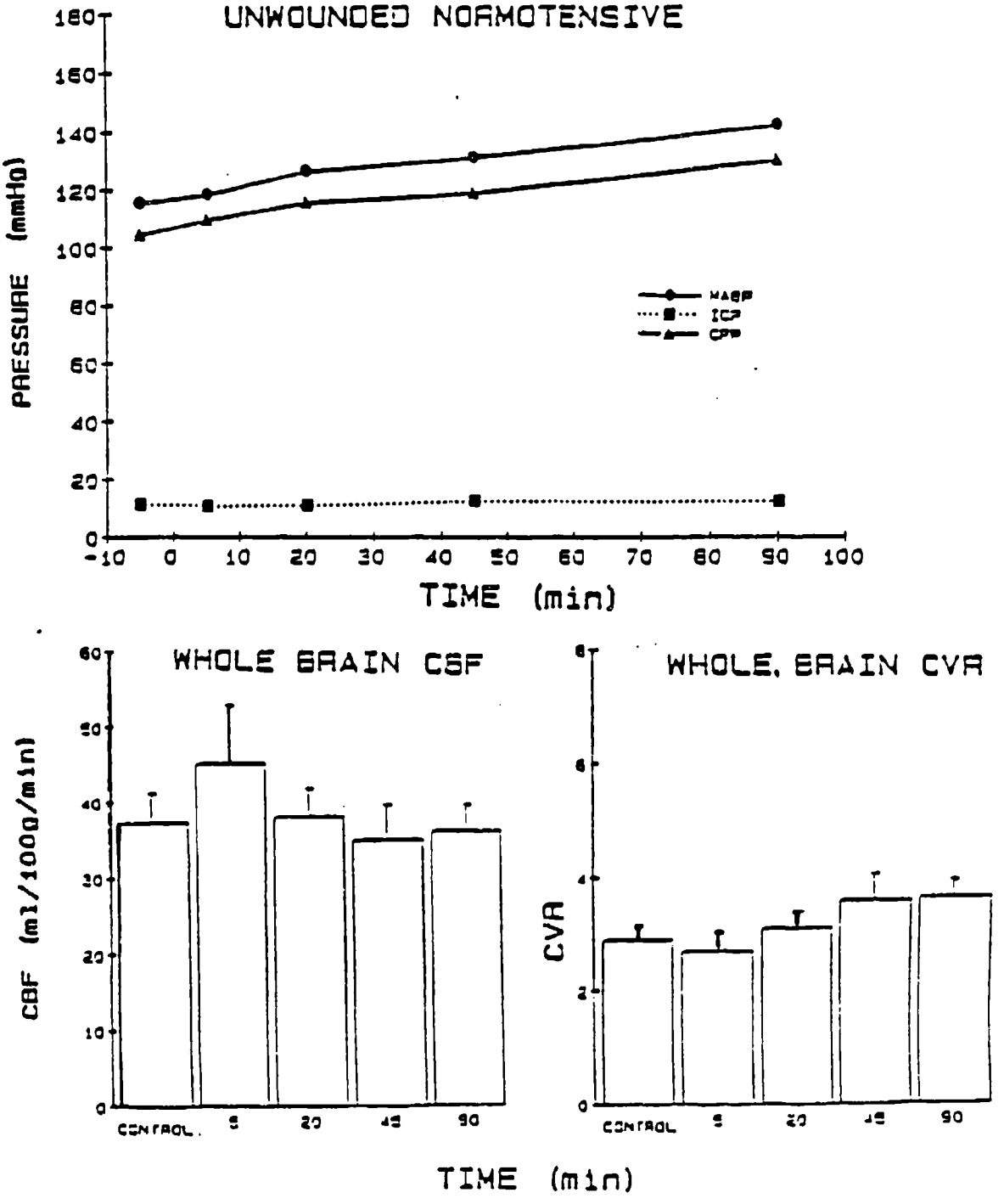

Fig I-A: Alterations in systemic and intracranial pressures (upper graph) and in total CBF and CVR (lower bargraph) in unwounded normotensive cats (control) during 5 consecutive measurements over a period of 100 min. All physiological parameters measured remained relatively stable during the entire period of experimentation.

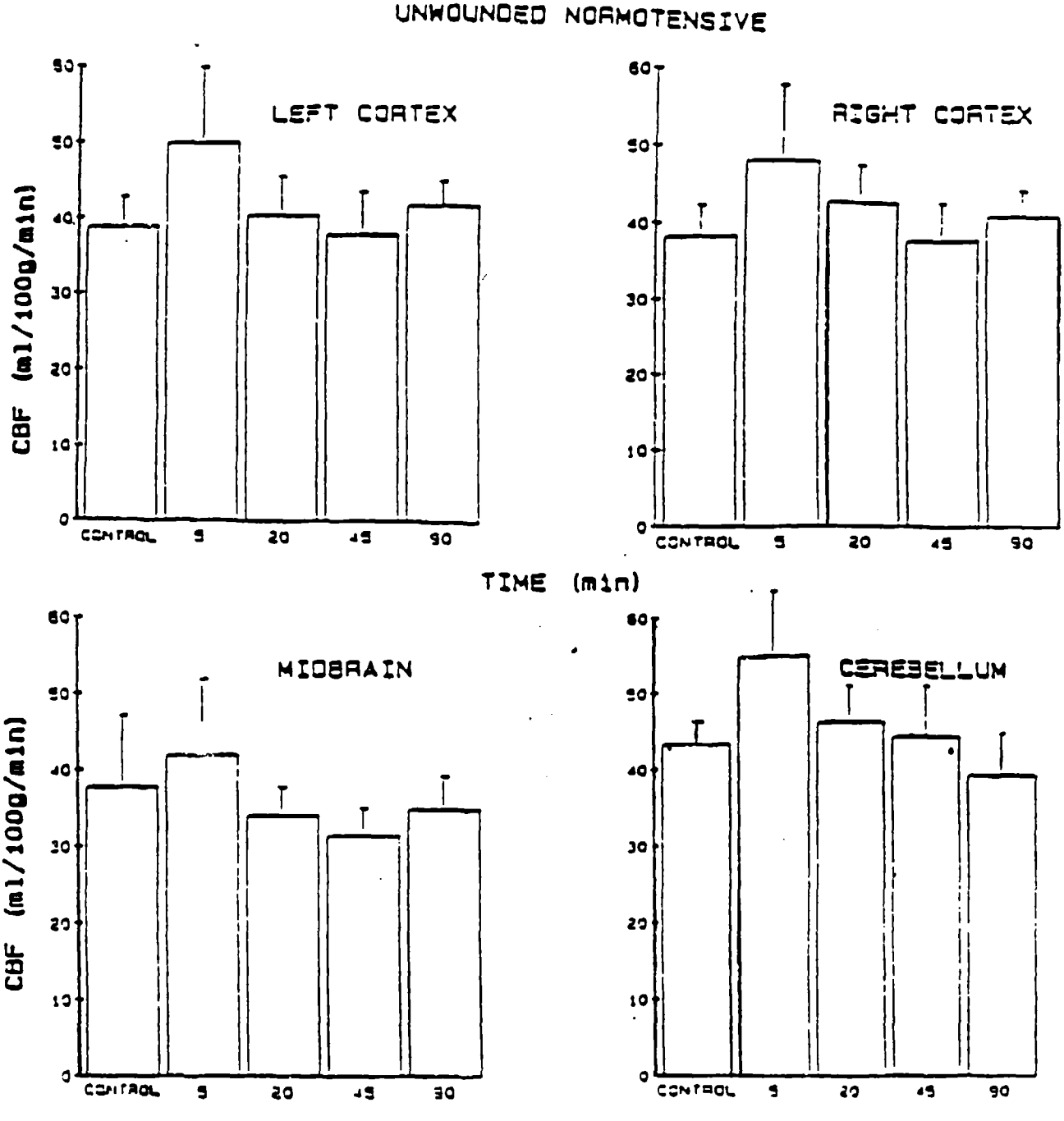

Fig I-8: Changes in rCBF of 4 selected structures in unwounded normotensive cats during 5 consecutive CBF measurements. No significant differences in rCBF were found either between left-right structures or among different measurements over the 100 min period of experimentation.

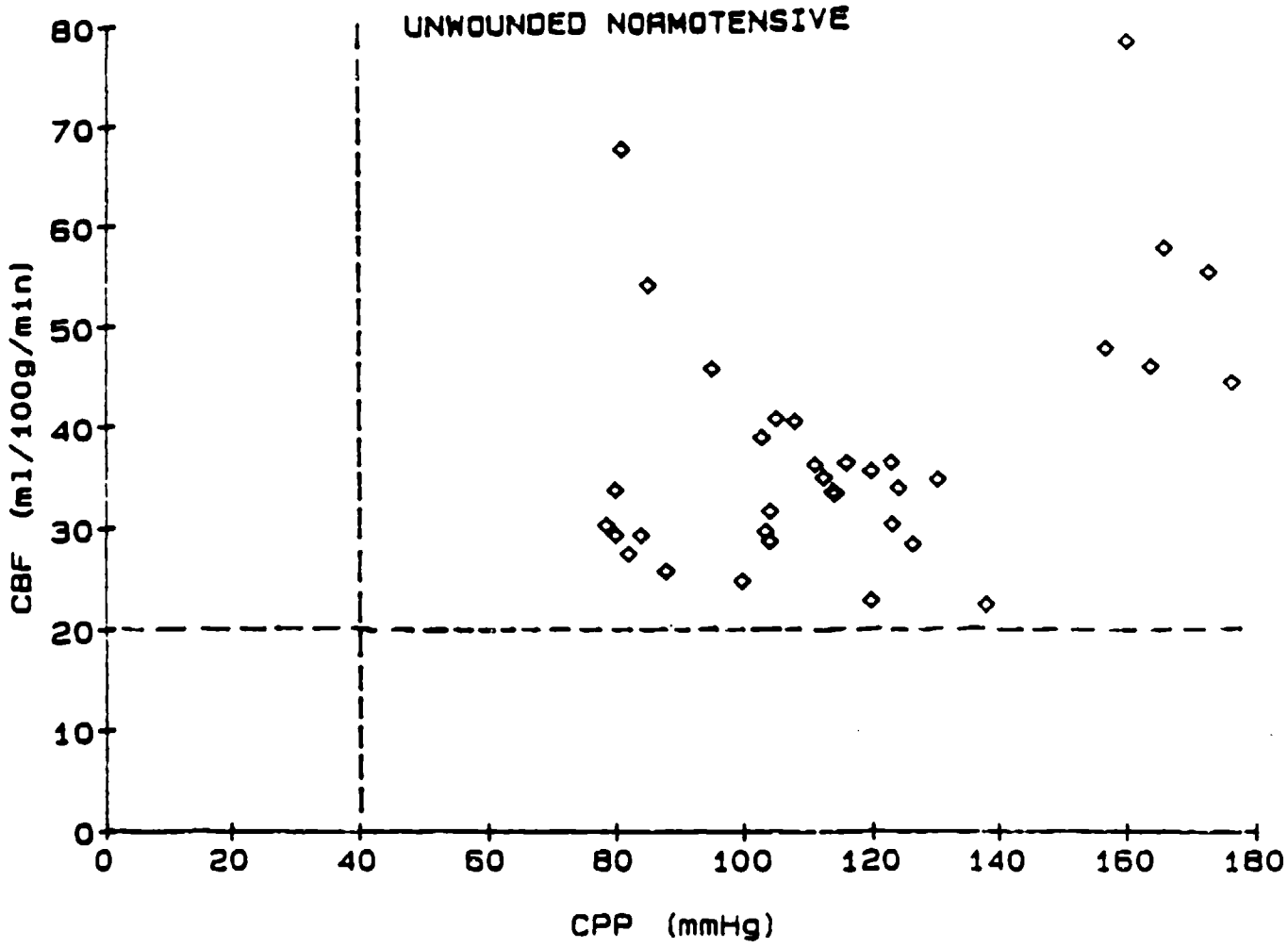

Fig I-C: Flow-pressure relationships in unwounded normotensive cats Values are clustered above theoretical dashed lines defining critical levels for CBF and CPP which usually allow autoregulation and normal functional activity.

GROUP II, WOUNDED NORMOTENSIVE CATS (N=7): Cats in this group remained normoxic and normocapnic (PO_2 of 126 to 133 mmHg; PCO_2 of 29 to 32 mmHg on the average) during the entire period of experimentation (Table II-A). Twenty min after wounding, however, arterial pH decreased from 7.37 to 7.31 ($[H^+]$ increased from 42 nmol/l to 57 nmol/l). This level of metabolic acidosis persisted 90 min post-wounding. The BMW-induced metabolic acidosis was purposely left uncorrected in order to simulate the combat situation where a brain wounded individual's metabolic acidosis might remain untreated for a considerable period of time.

The upper trace of Fig II-A shows pre- and post-wounding changes in MABP, ICP and CPP. The control MABP of 134 mmHg was significantly increased immediately after BMW, reaching an average peak of 177 mmHg. Within a few minutes the MABP returned to normotensive levels (114-128 mmHg) for the remainder of the experiment. The ICP on the other hand, was increased from a control level of 9 mmHg to 64 mmHg within 5 min after BMW. It then declined to approximately 45 mmHg between 20 to 90 min post-BMW. Corresponding CPPs were reduced from a control of 125 mmHg to 60-84 mmHg after wounding. The bargraphs in Fig II-A illustrate pre- and post-wounding alterations in total CBF and CVR. The rCBFs in the left cortex, structures around the wound track (periwound), midbrain and cerebellum are illustrated in Fig II-B. BMW produced a gradual reduction in both total CBF and rCBFs which became significant at 45 min (Table II-B). Total CVR appeared to be reduced 5 minutes after wounding but this reduction was not statistically significant. By 90 minutes CVR was very close to control values. CBF fell even though CPP remained above 60 mmHg. Post-wounding blood flow changes seen in individual structures were of different magnitudes and occurred at different times after injury. For instance, cortical structures showed a significant reduction in blood flow starting 20 min after wounding, while the periwound CBF remained at control levels at this time. Periwound CBF did not show a decriment until 45 minutes after wounding and this decrease did not become significant until 90 minutes after wounding. No significant reduction in flow occurred in midbrain, cerebellum, hippocampus, reticular formation and pons during the entire 90 min post-wounding period (Fig II-B, Table II-B). Individual CBF-CPP relationships in the wounded normotensive cats are presented in Fig II-C. Unlike unwounded normotensive cats (Fig 1-C), the individual values in the wounded cats (Fig II-C) were scattered through a larger range of CPPs and CBFs. Normal CBFs were sometimes observed when the CPPs were much below 40 mmHg, but, in general, CBFs tended to fall even though CPPs generally remained within the theoretical autoregulatory range (> 40-60 mmHg). The CBF in some cases was reduced when CPP values were even greater than 60 mmHg. This may indicate lack of autoregulatory ability following BMW.

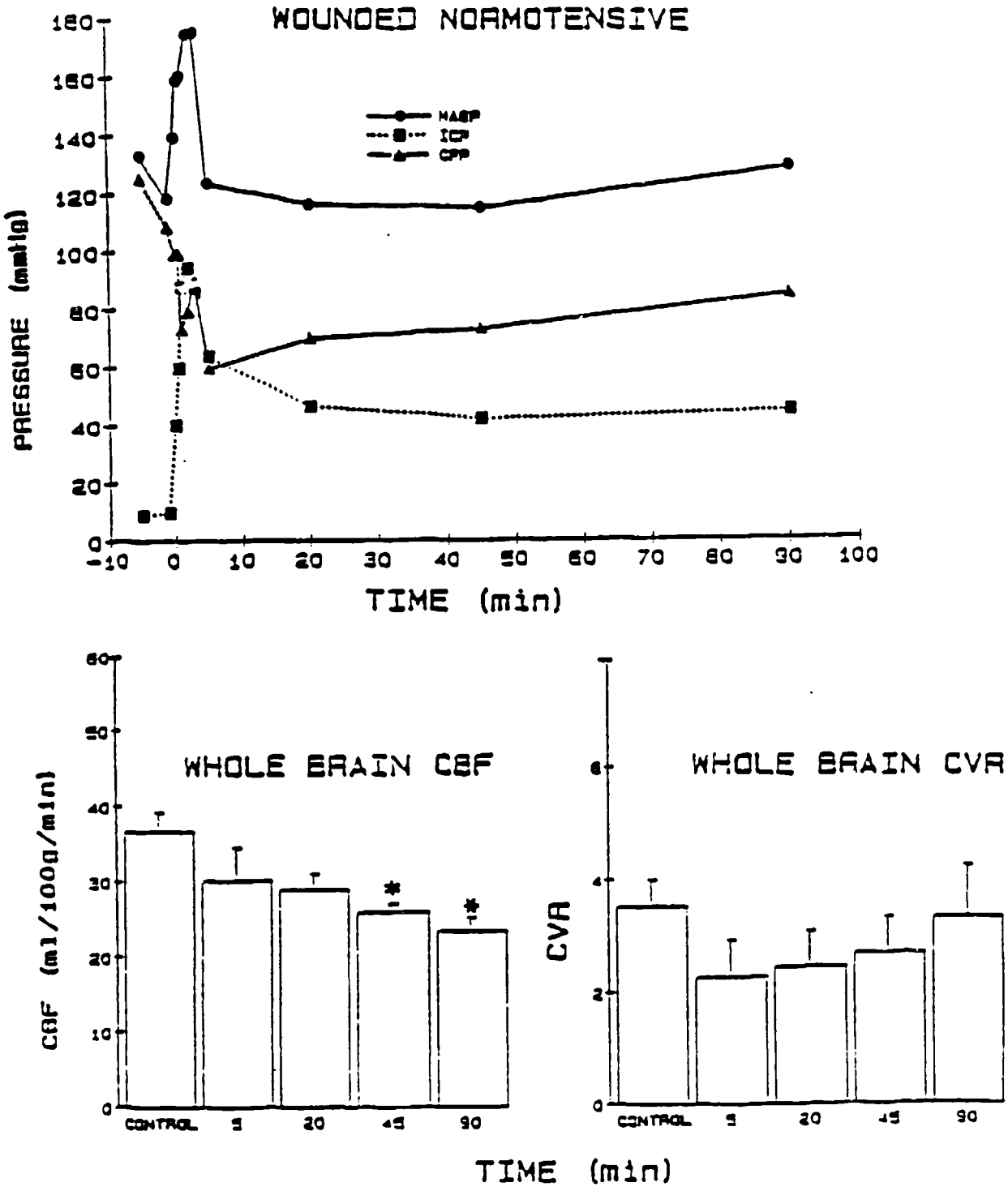

Fig II-A: Alterations in systemic and intracranial pressures and in total CBF and CVR in wounded normotensive cats during 90 min post-wounding. * Significant as compared to control; $p<0.05$.

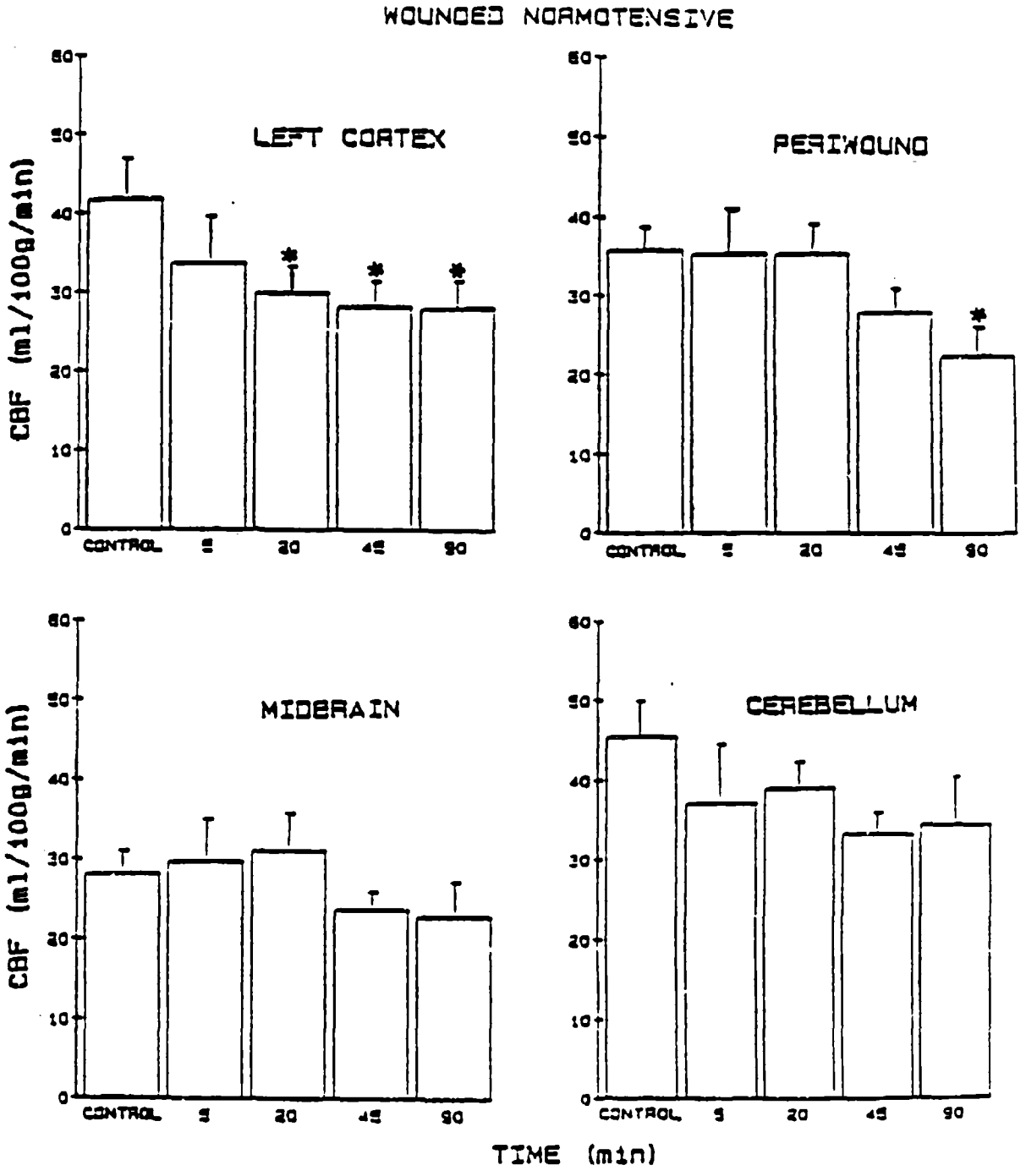

Fig II-B: Changes in rCBF of 4 selected structures in wounded normotensive cats during 90 min after wounding. Post-wounding reduction in blood flow is not uniform in different brain areas. * Significant as compared to control; $p<0.05$.

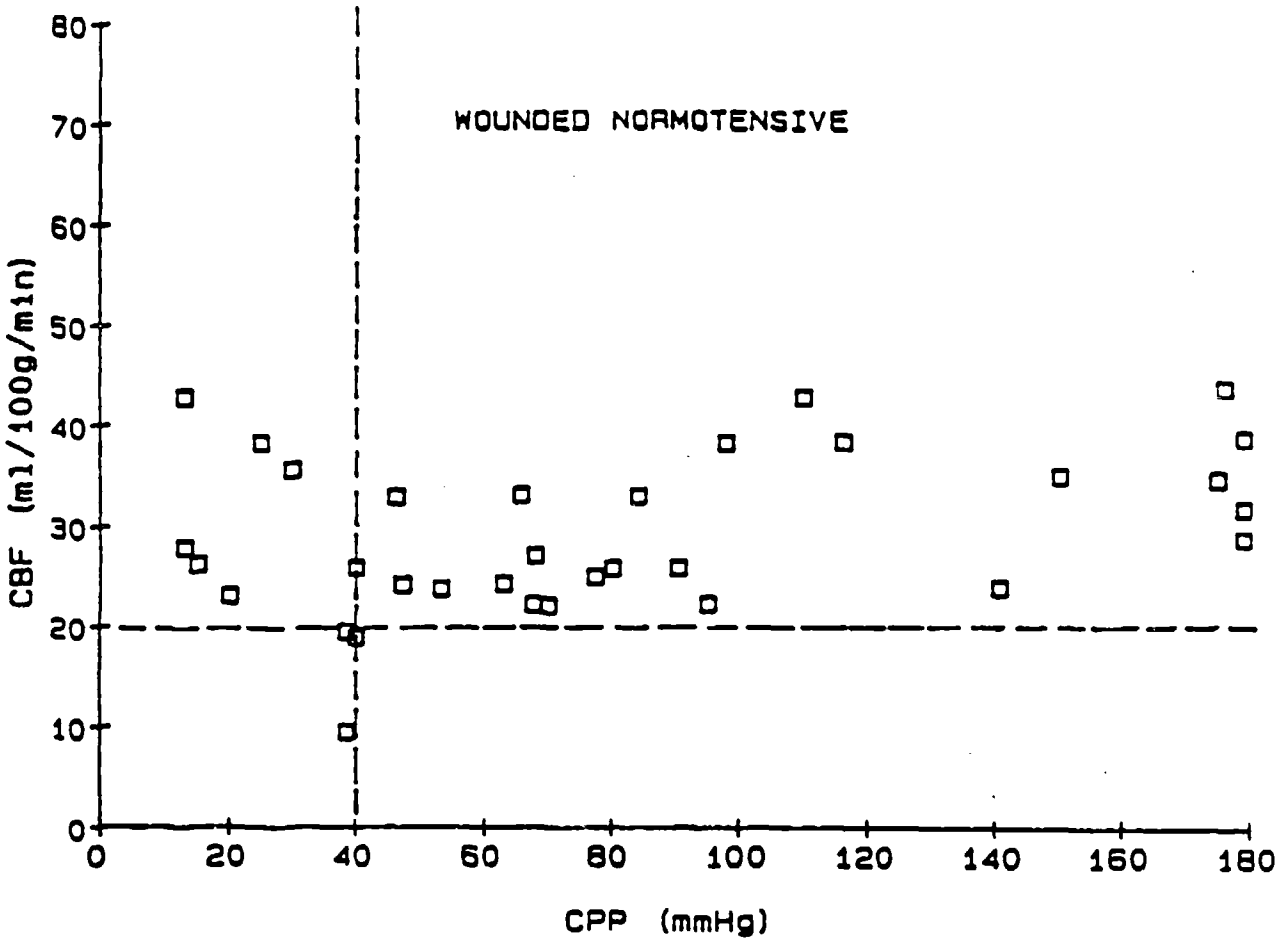

Fig II-C: Flow-pressure relationship of individual cats in wounded normotensive group during a control and 4 post-wounding measurements. The dashed lines define theoretically critical levels of CBF and CPP beyond which autoregulation/functional activity may be impaired. 2 cats died around 80 min after BMW and had only 4 CBF measurements

ALTERATIONS IN EEG FOLLOWING BMW: Concurrent with BMW the normal EEG pattern of irregular high and low amplitude of fast and slow frequency waves changed to a synchronized high or low amplitude slow wave activity (Fig 1). This EEG pattern was soon replaced by gradually decreasing amplitude consisting mostly of slow wave activity which deteriorated in cats showing extreme reductions in CBF (below 15 ml/100g/min). These characteristic changes in EEG up to 2 hours after wounding are shown in Fig 2. In cats whose ICPs rapidly declined to levels below 40 mmHg, the EEG slowly recovered to a more normal pattern but with persisting low amplitudes in all frequencies. When the EEG became clearly flat after wounding, rCBFs were determined to be close to zero. In subsequent studies therefore, when a completely flat EEG was observed, the experiment was stopped and data excluded from further consideration.

GROUP III, UNWOUNDED HYPOTENSIVE CATS (N=8): Cats in this group remained normoxic (PO_2 125 to 130 mmHg) and normocapnic (PCO_2 28-33 mmHg) during hemorrhagic hypotension (HH) and reinfusion (Table III-A). The volume of blood shed in this group was between 50 ml and 130 ml in individual cats constituting up to 30% of their blood volume (35). pH decreased from a control of 7.39 to 7.21 when the animals were bled and MABP fell; ($[H^+]$ increased from a control of 41 nmol/l to 51 and 63 nmol/). These cats developed no significant changes in ICP. Thus, CPPs linearly followed the reductions in MABP. Total CBF did not change in these cats despite severe hypotension. It was maintained by CVR reduction (Fig III-A). CBF autoregulation clearly occurred.

Reinfusion of shed blood, which started 45 min after the onset of bleeding, returned both MABP and CPP to the normotensive range and restored the CVR back to normal by 90 min. Reinfusion did not significantly improve the arterial metabolic acidosis. pH remained 7.25 45 minutes after the beginning of reinfusion; ($[H^+]$=57 nmol/l). Cortical rCBFs tended to show a reduction in flow with HH but these reductions were not statistically significant. (Fig III-B). All other brain structures unequivocally maintained their blood flow at all levels of hypotension and after reinfusion (Table III-B).

One cat in this group was also used for evaluation of shunting and demonstrated A-V (sagittal sinus) shunting of less than 0.5 % on average.

The CBF-CPP relationship of the individual measurements for this group is demonstrated in Fig III-C. Large number of normal CBFs over a wide range of CPPs clearly indicates that pentobarbital anesthetized cats with intact brains are capable of autoregulating their CBF at least down to a CPP of 30 mmHg. Cortical rCBFs tended to show a reduction in flow with HH but these reductions were not statistically significant.

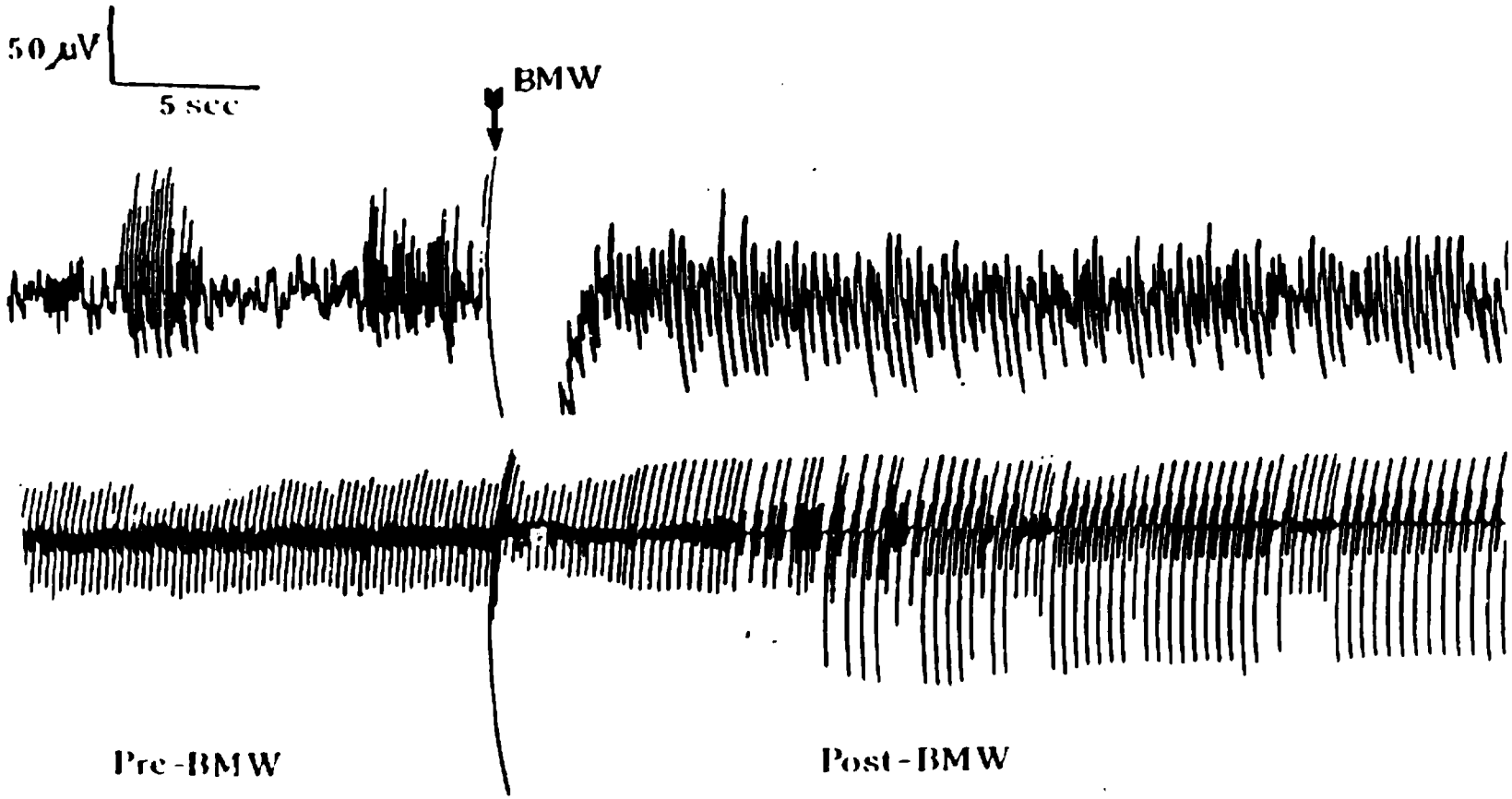

Fig 1: Alterations in EEG and ECG immediately before and after BMW (1.4 J) in a noromotensive anesthethized paralyzed cat. A high amplitude slow wave activity usually develops immediately after wounding which lasts for a few min before it is replaced by low amplitude waves. The ECG arryhthmias are developed within seconds after BMW and will continue for 3-4 min providing the animal is ventilated.

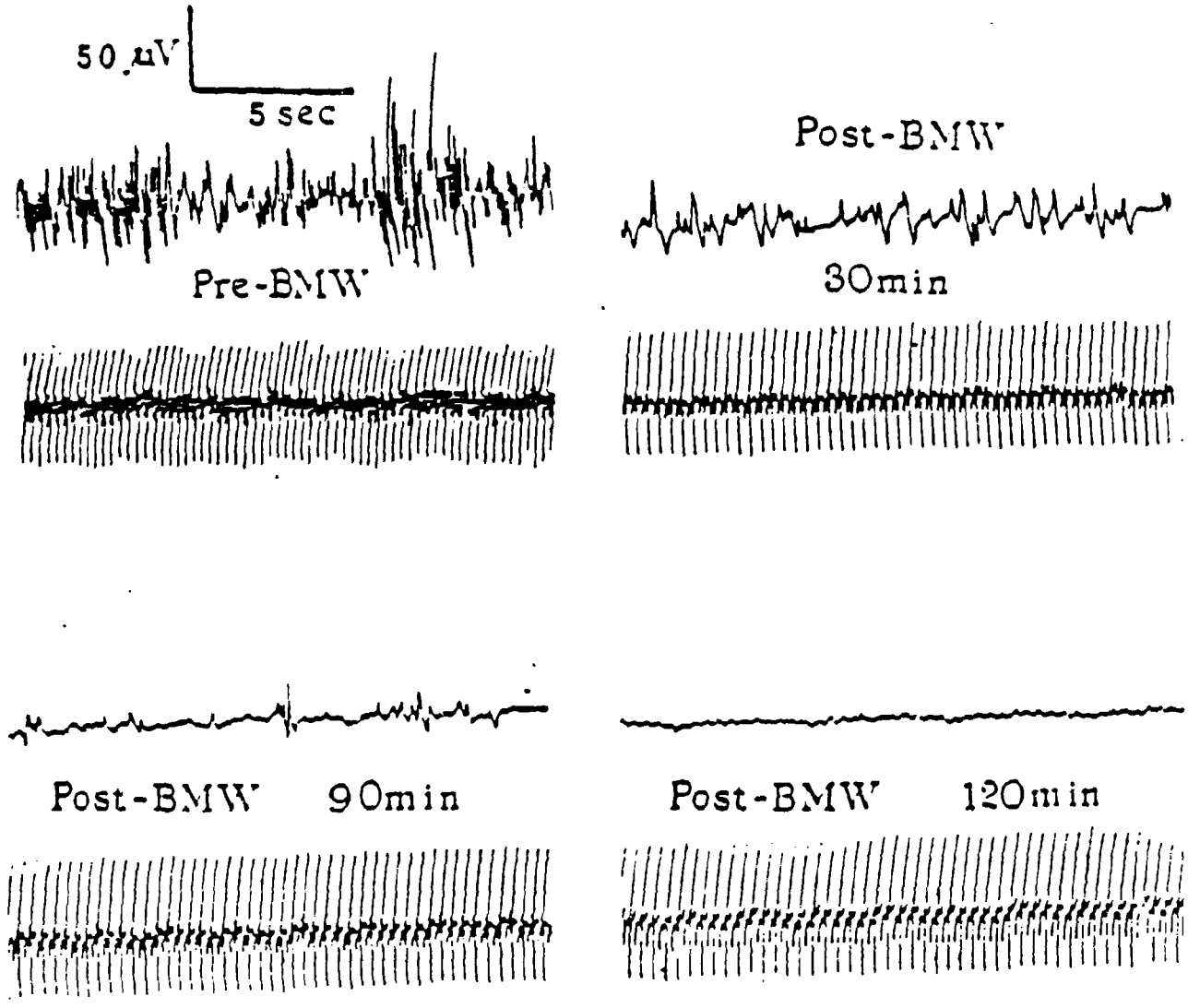

Fig 2: Alterations in EEG and ECG up to 2 hours after BMW (1.4J) in a normotensive anesthetized paralysed cat. Note a gradual reduction in frequency and amplitude of EEG waves, typical of a wounded cat which usually does not recover from injury. The CBF at 90 min post-wounding is 15 ml/100g/min, a value believed to be inadequate for cortical cerebral functional activity.

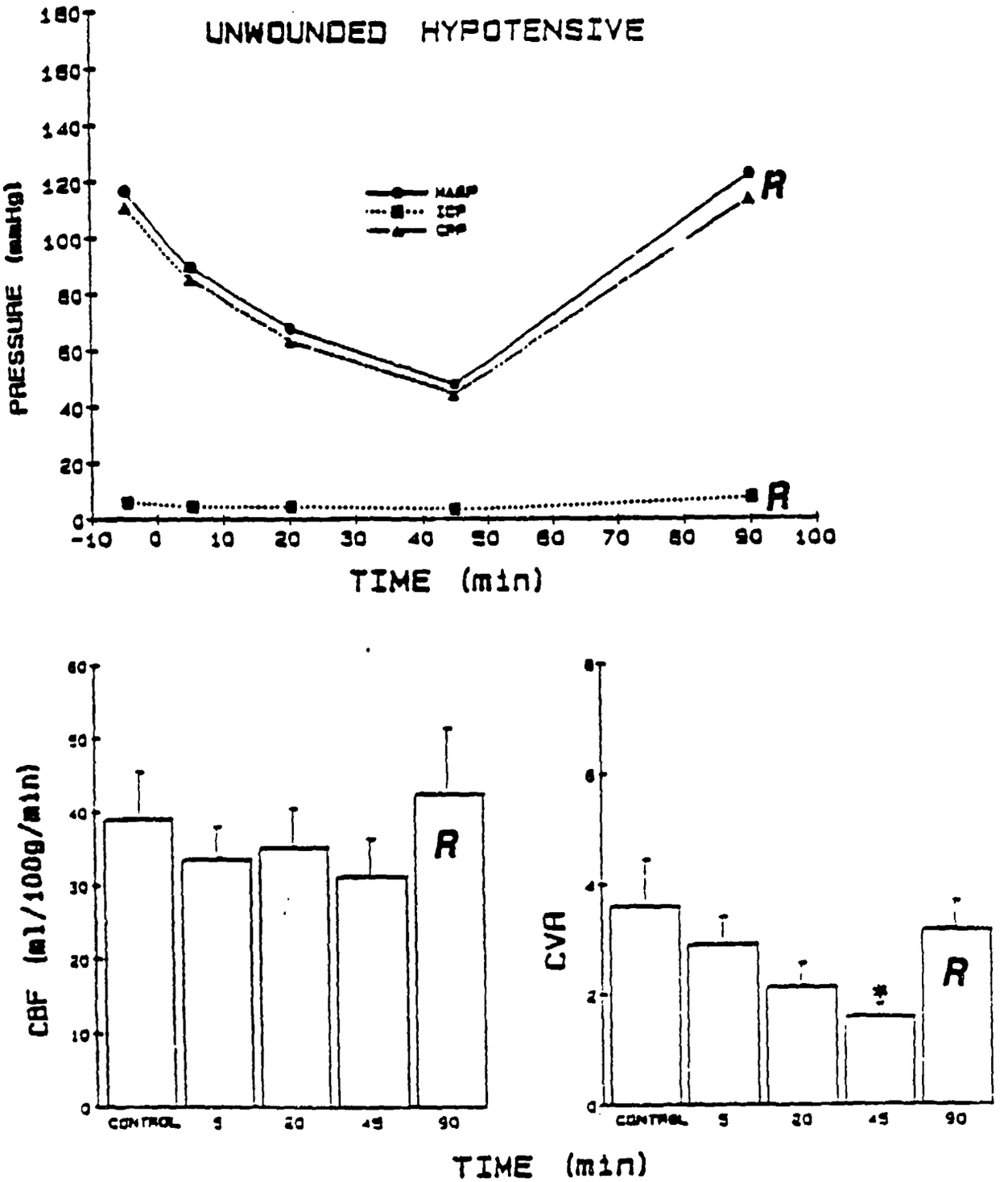

Fig III-A: Alterations in systemic and intracranial pressures and in total CBF and CVR in unwounded hypotensive cats at 3 steady-state levels of hypotension and after reinfusion (R). Autoregulation remained intact down to a MABP of 45 mmHg as judged by a maintained CBF associated with gradual reductions in CVR. * Significant as compared to control; $p<0.05$.

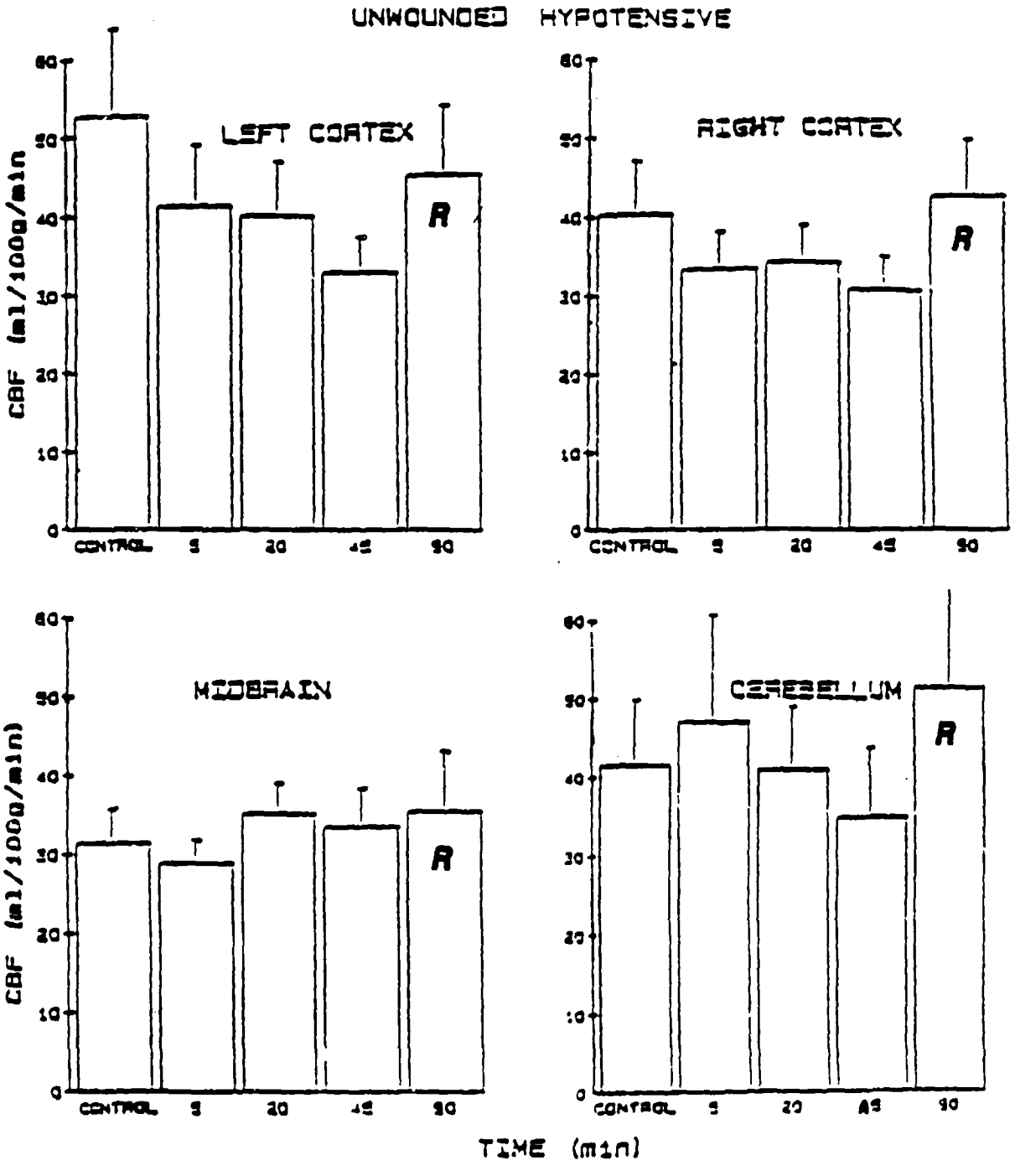

Fig III-B: Changes in rCBF of 4 selected structures in unwounded hypotensive cats at 3 steady-state levels of hypotension (5, 20, 45 min) and after reinfusion (90 min). R=After reinfusion.

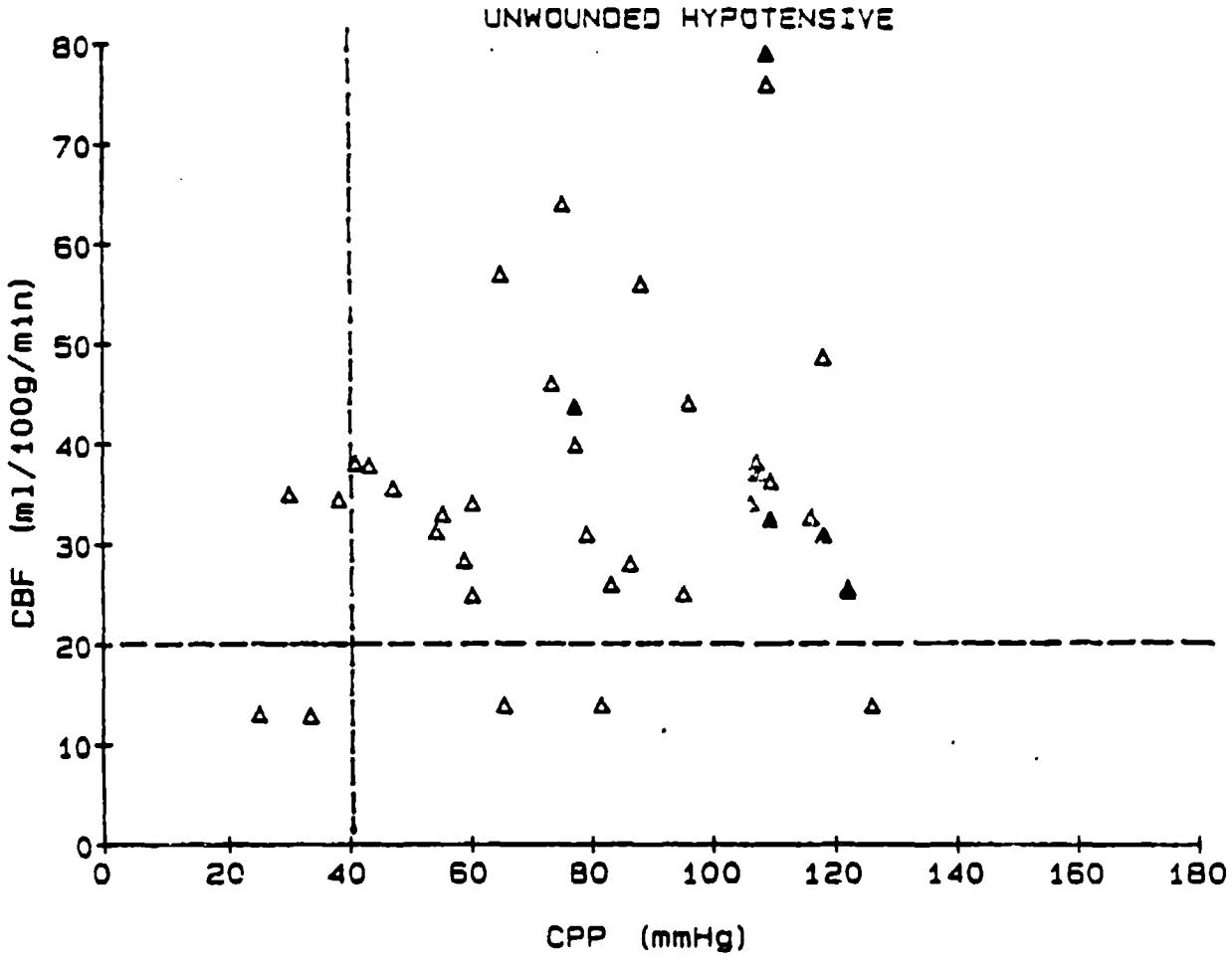

Fig III-C: Flow-pressure relationship of individual cats in unwounded hypotensive group at 3 levels of hypotension and during normotensive conditions before bleeding and after reinfusion (▲). Most data points show normal CBF even at relatively low CPPs indicating intact autoregulation. One animal had persistently low CBF but autoregulated nevertheless (18 to 15 ml/100g/min). Reinfusion was not attempted in two cats.

GROUP IV, WOUNDED HYPOTENSIVE CATS (N-10):

Cats in this group remained normoxic (PO_2 of 121-126 mmHg) throughout the experimentation period. The arterial PCO_2, however, was significantly reduced during severe hypotension from 32 mmHg before wounding to 24 mmHg at 45 min post-wounding (Table IV-A). A significant metabolic acidosis was simultaneously observed; pH decreased from 7.37 to 7.26; ($[H^+]$ increased from 46 to 65 nmol/l).

The upper trace of Fig IV-A shows the average MABP, ICP and CPP for all 10 animals during post-wounding HH and reinfusion. The mean ICP was increased from a control of 6 mmHg to 60 mmHg 5 min after wounding. The mean CPP was correspondingly reduced to 46 mmHg and was associated with a 45% reduction in total CBF (Fig IV-A). The reduction in CVR was apparently not adequate to prevent CBF reduction. The fall in mean CBF with reduction either in MABP or CPP indicates complete failure of mechanical CBF regulation for the group as a whole. rCBF reduction in all structures also showed severe decreases but CBF tended to be better preserved in the brain stem (Fig IV-B).

With reinfusion of shed blood the ICP increased greatly from a mean of 31 mm Hg to 60 mmHg. Mean CPP increased only slightly. Total CVR was markedly increased, however, rCBFs became even further reduced (Table IVB).

The CBF-CPP relationship of individual measurements in wounded hypotensive cats is demonstrated in Fig IV-C.

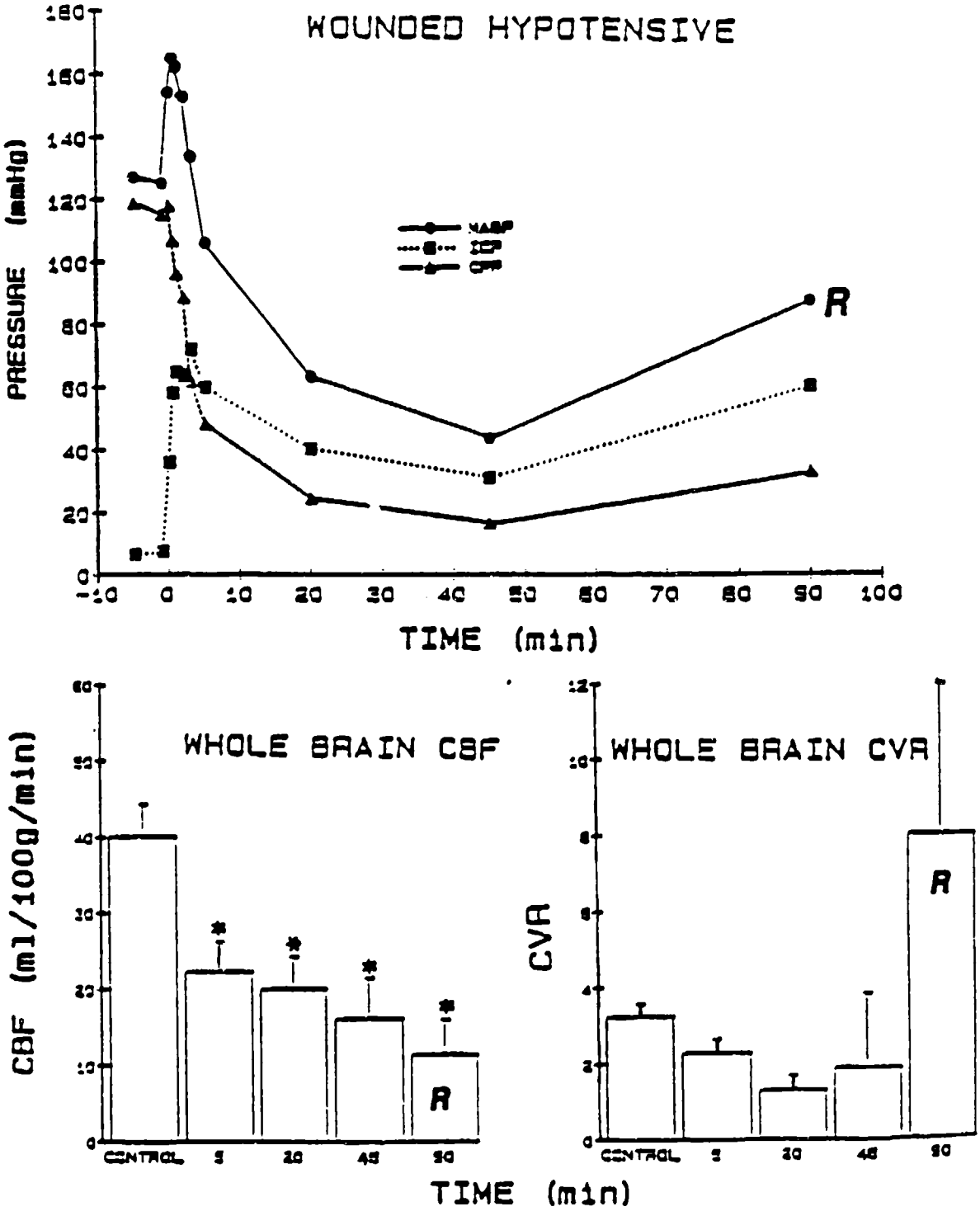

Fig IV-A: Alterations in systemic and intracranial pressures and in total CBF and CVR in wounded hypotensive cats at 3 post-wounding levels of hypotension and after reinfusion (R). Autoregulation was impaired (reduced CBF) as soon as BMW was associated with a mild hemorrhagic hypotension (5 min). * Significant as compared to control; $p<0.05$.

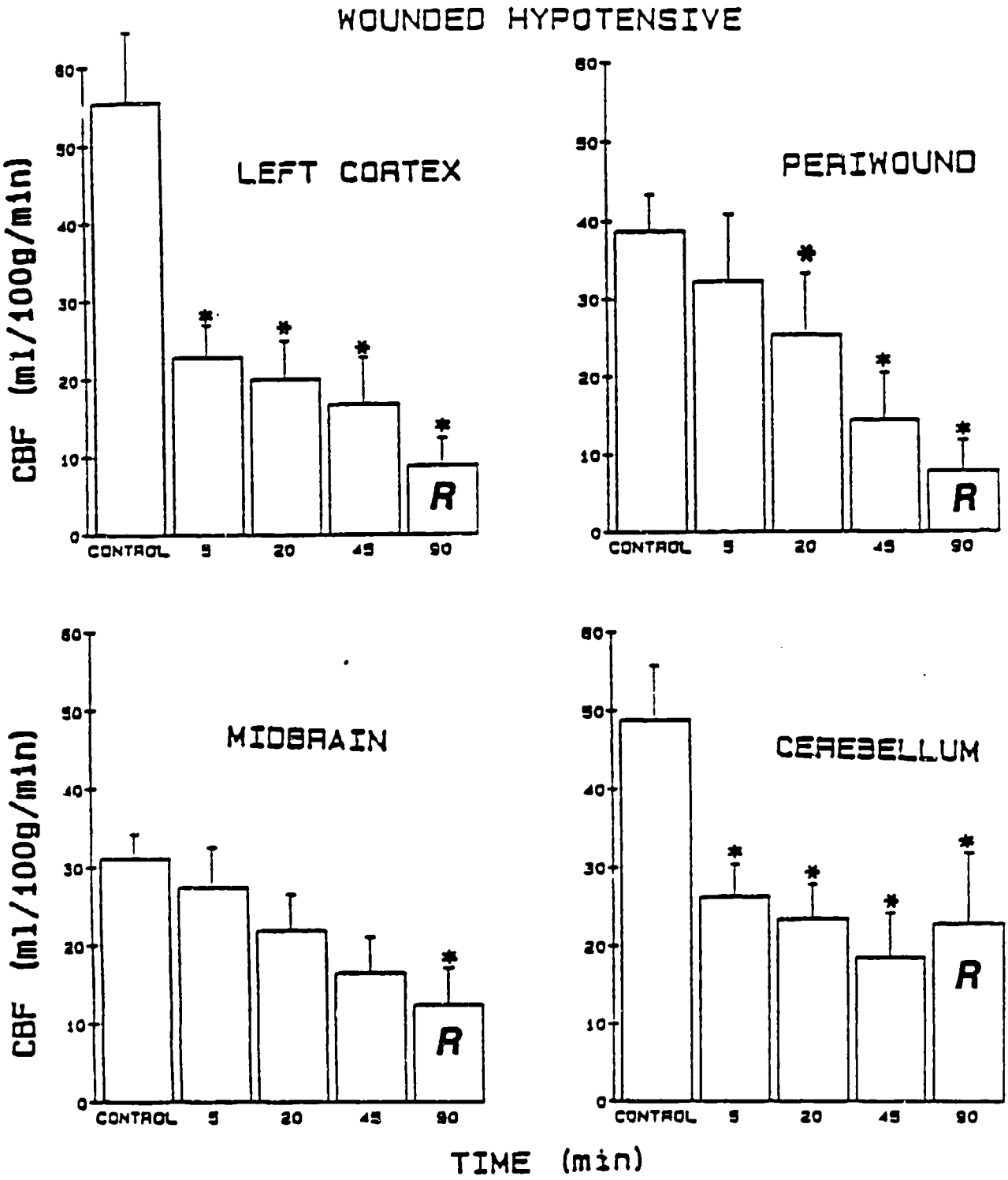

Fig IV-B: Changes in rCBF of 4 selected structures in wounded hypotensive cats at 3 post-wounding levels of hypotension (5, 20, 45 min) and after reinfusion (90 min). Autoregulation was impaired in all structures by 20 min post-wounding. Reinfusion (R) further reduced rCBF in most structures except the cerebellum. * Significant as compared to control; $p<0.05$.

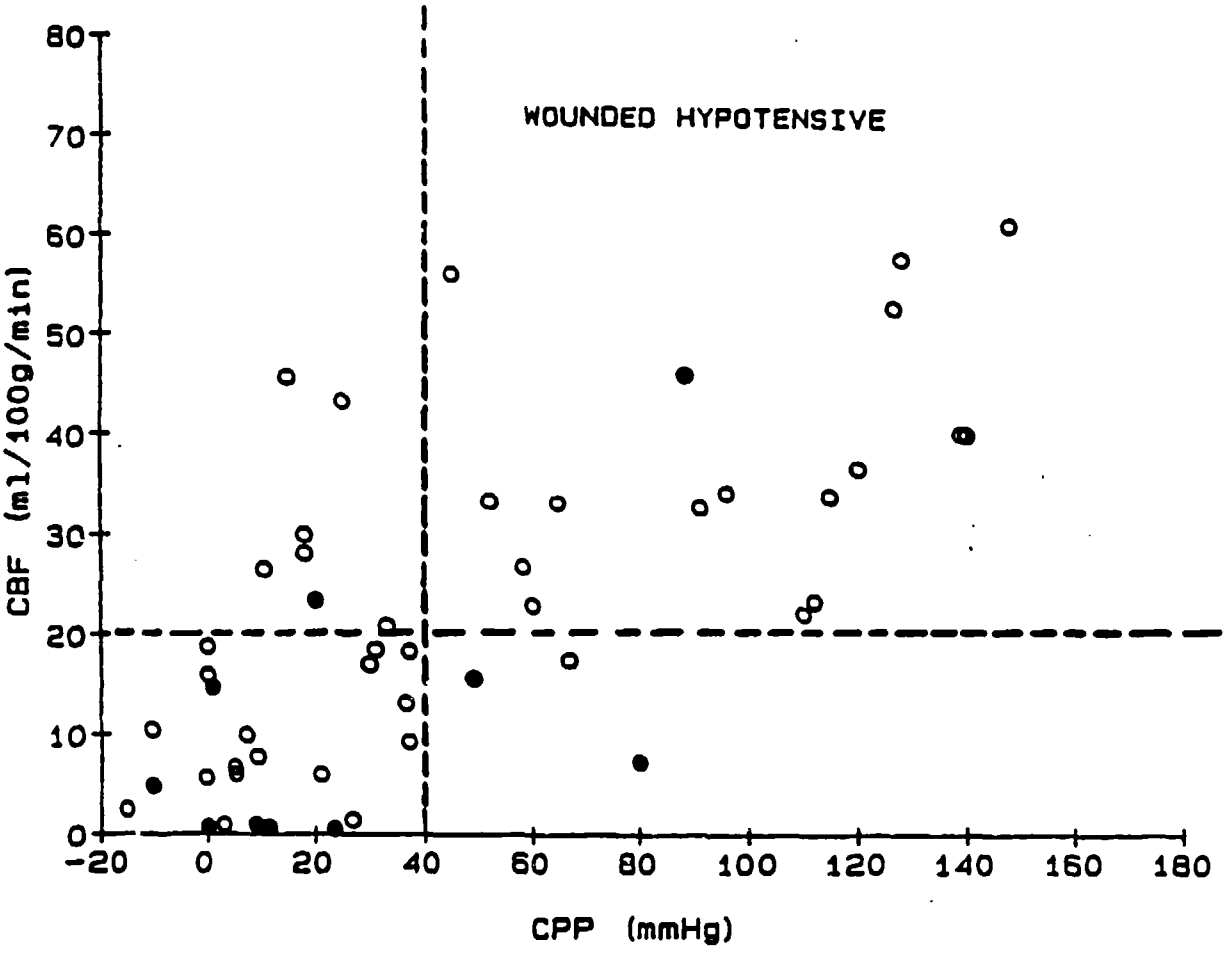

Fig IV-C: Flow-pressure relationship of individual wounded hypotensive cats during pre-wounding period, at 3 levels of hypotension and following reinfusion (●). High and low CBF data points, scattered below the CPP line of 40 mmHg, may represent two distinct cerebrovascular responses, namely "autoregulating" and nonautoregulating. Reinfusion, however, abolished any autoregulatory ability in most cats even when CPPs were relatively increased.

The existence of both relatively normal and very low CBFs at CPPs lower than 40 mmHg suggested two different cerebrovascular reactions to post-wounding hypotension. Review of the concomitant EEG data also appeared to indicate a bimodel response to brain wounding plus simultaneous hemorrhagic hypotension. Some animals maintained relatively normal EEGs (Fig 3) after injury while others did not (Fig 4). The former had much higher mean CBFs after wounding and HH than did the latter. These differences suggested to us that this group of 10 cats really should be divided into two subgroups: four cats which maintained CBF despite brain wounding and simulataneous HH and 6 which did not. We have initially presented total group data in Figs IV A, B, and C because of experimental design and statistical considerations. MABP, ICP, CPP, EEG, and CBF differences between these two sub-groups as perceived by us are presented in Figs 3-7 and are summarized in Table 1.

Table 1

PERTINENT VARIABLES DISTINGUISHING CATS MAINTAINING POST-WOUNDING CBF FROM THOSE THAT DID NOT

	Maintaining CBF N=4		Not Maintaining CBF N=6	
Control	MABP	118 mmHg	MABP	135 mmHg
	ICP	3 mmHg	ICP	5 mmHg
	CPP	115 mmHg	CPP	130 mmHg
	CBF	37 ml/100g/min	CBF	42 ml/100g/min
	EEG	normal	EEG	normal
5 min Post Wounding	MABP	99 mmHg	MABP	112 mmHg
	ICP	41 mmHg	ICP	73 mmHg
	CPP	58 mmHg	CPP	39 mmHg
	CBF	35 ml/100g/min	CBF	14 ml/100g/min
	EEG	normal	EEG	reduced amplitude, frequency
45 min Post Wounding (Severe HH)	MABP	38 mmHg	MABP	45 mmHg
	ICP	16 mmHg	ICP	40 mmHg
	CPP	22 mmHg	CPP	5 mmHg
	CBF	31 ml/100g/min	CBF	7 ml/100g/min
	EEG	normal	EEG	almost flat
90 min Post Wounding	MABP	82 mmHg	MABP	91 mmHg
	ICP	58 mmHg	ICP	62 mmHg
	CPP	25 mmHg	CPP	29 mmHg
	CBF	22 ml/100g/min	CBF	4 ml/100g/min
	EEG	slightly reduced amplitude	EEG	flat

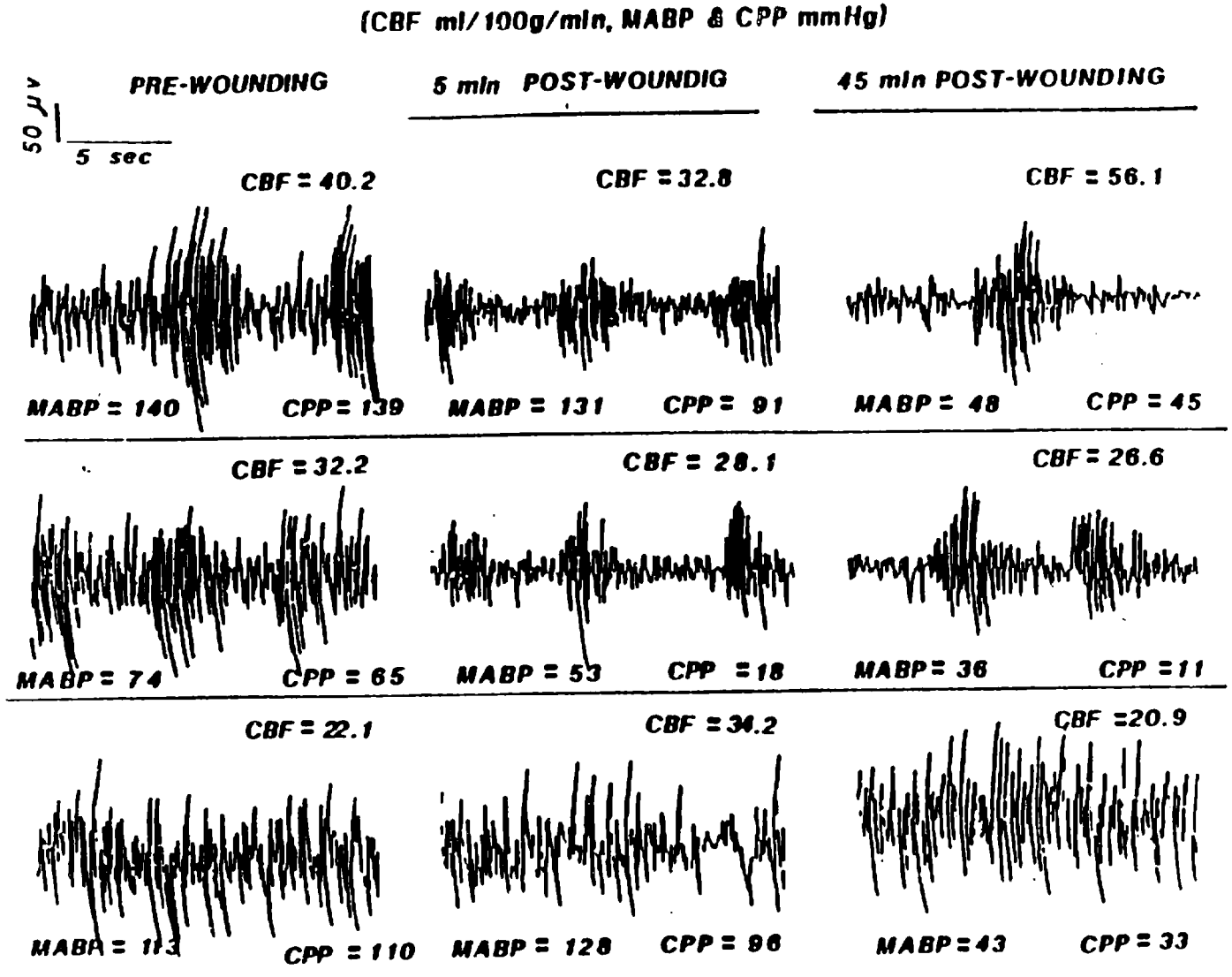

Fig 3: Alterations in EEG, total CBF, MABP and CPP in 3 out of 4 wounded hypotensive cats which showed a relatively normal pattern of EEG and maintained their CBF level despite extreme reductions in CPP. These wounded hypotensive cats which were considered as "autoregulating" developed a significantly lower CBF and EEG activity following blood reinfusion.

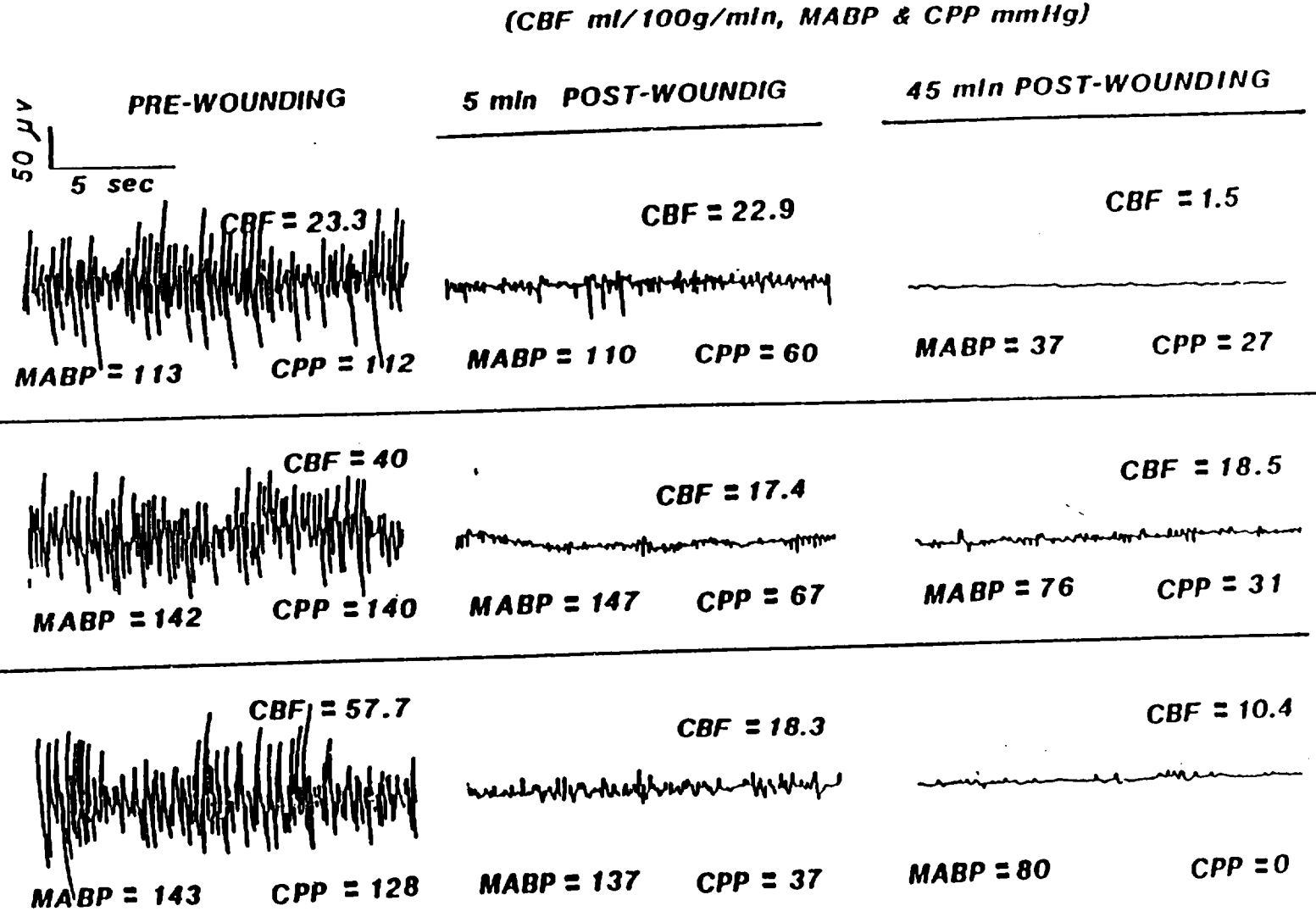

Fig 4: Alterations in EEG, total CBF, MABP and CPP in 3 out of 6 wounded hypotensive cats which showed drastic reductions in CBF and EEG activity 5 min after wounding despite CPPs of 37 to 67 mmHg. These nonautoregulating cats also failed to increase their CBF and EEG activity after blood reinfusion.

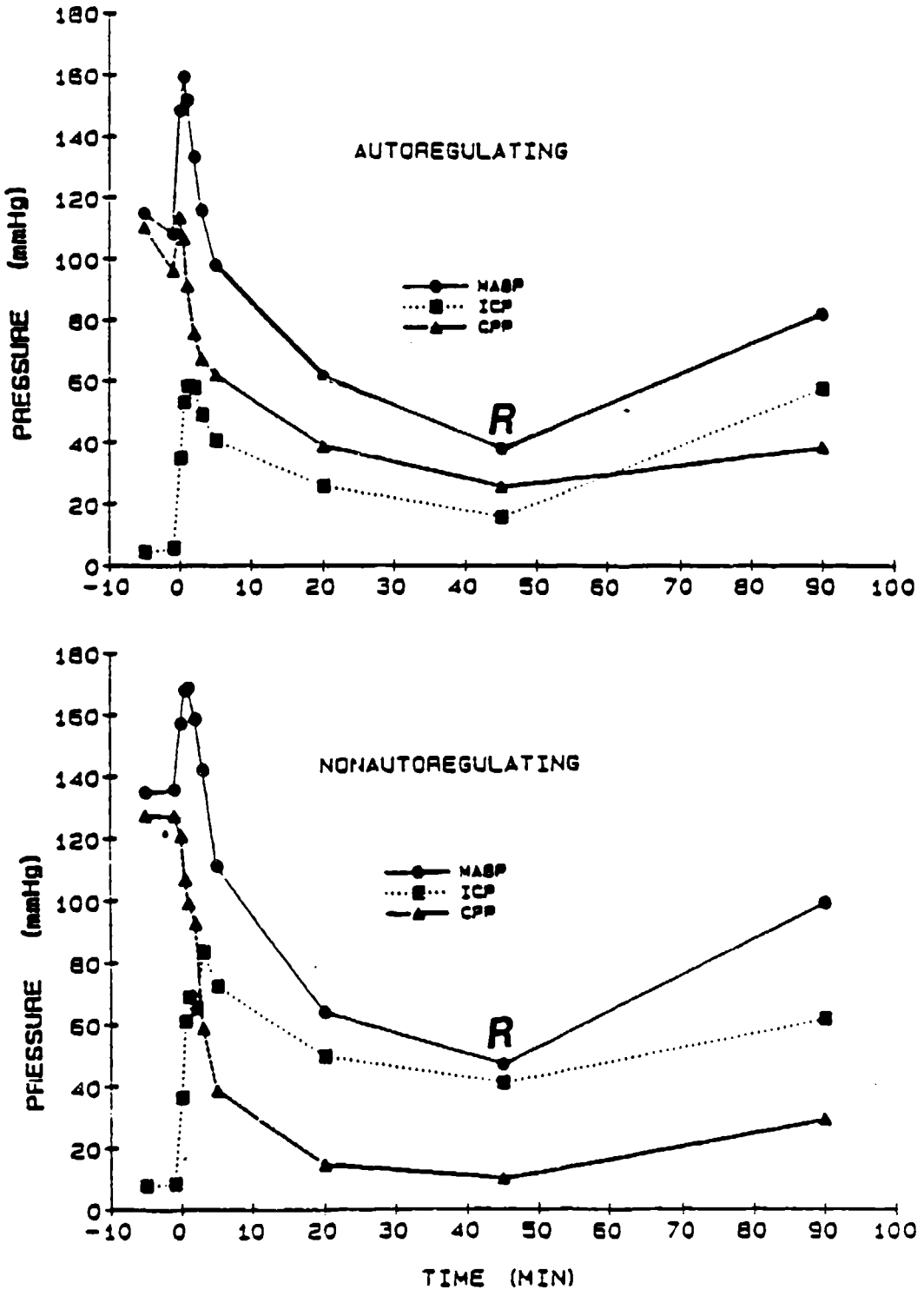

Fig 5: Changes in systemic and intracranial pressures in "autoregulating" and nonautoregulating wounded hypotensive cats. Note that in "autoregulating" cats the ICP levels were less than corresponding CPP values before reinfusion, whereas the post-wounding ICPs in nonautoregulating cats always exceeded the corresponding CPPs. R=Start of reinfusion.

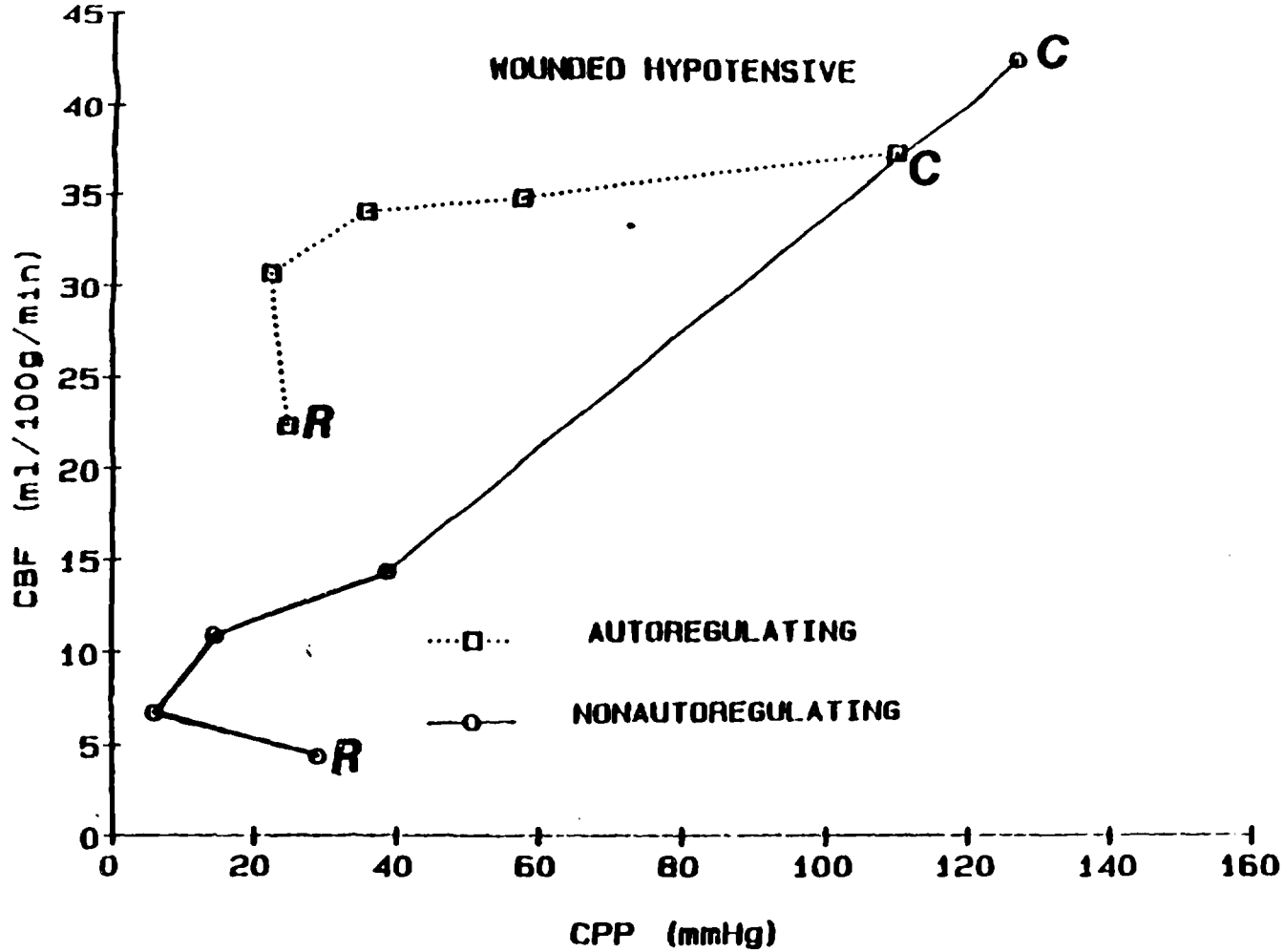

Fig 6: Average CBF-CPP relationships in two "autoregulating" and nonautoregulating wounded hypotensive subgroups. The four "autoregulating" cats still maintained a relatively normal CBF down to a mean CPP of ~25mmHg 45 min after wounding. Reinfusion of blood failed to raise CPP owing to concomitant ICP elevation reducing CBF further.The nonautoregulating cats (n=6) developed a rapid reduction of CPP to about 40 mmHg 5 min after wounding and CBF was reduced by 60%. This represents total loss of autoregulatory ability. C=Control values before BMW/bleeding; R=After completion of reinfusion.

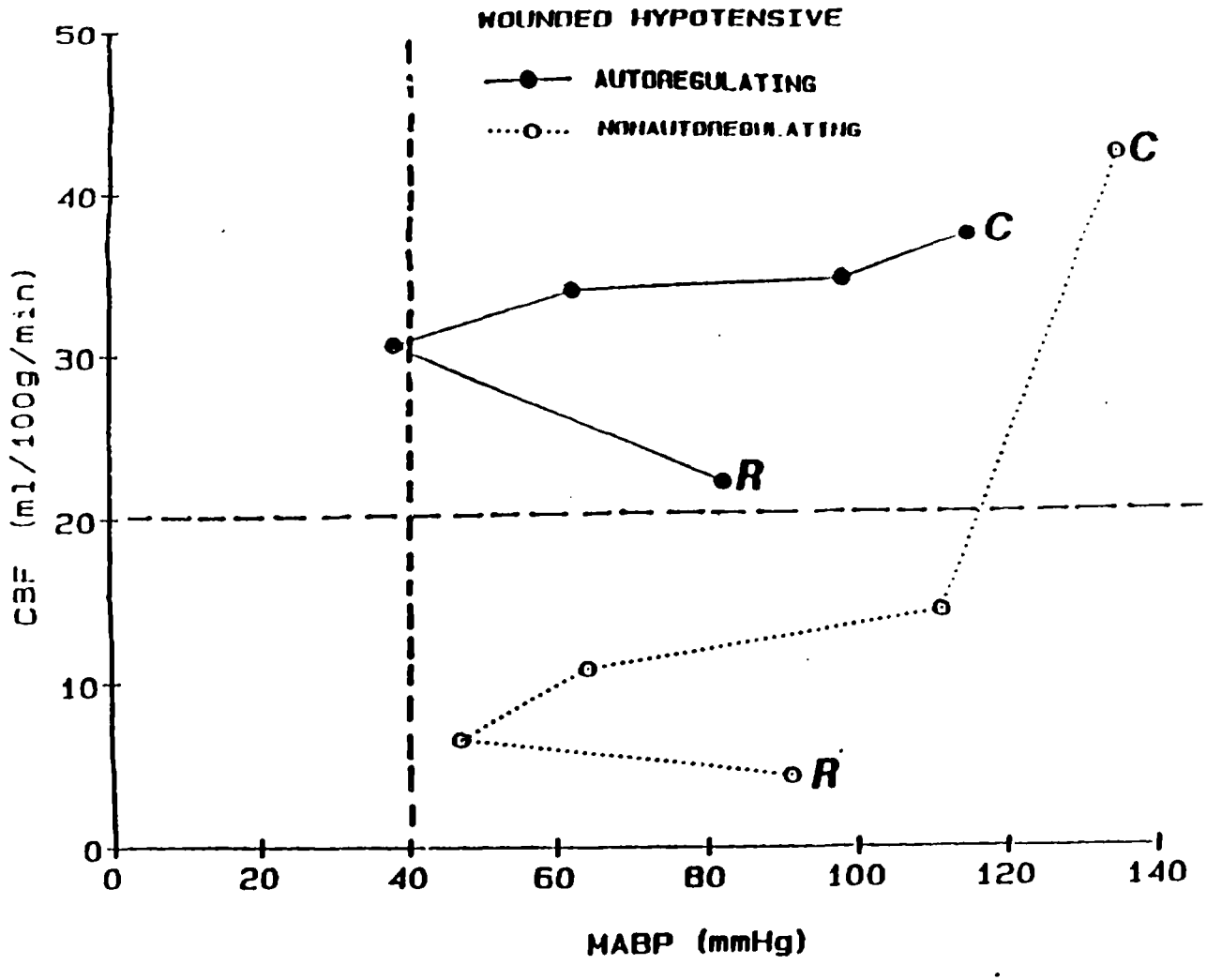

Fig 7: CBF-MABP relationships in wounded hypotensive "autoregulating" and non-autoregulating cats. The "autoregulating" cats had a relatively adequate level of CBF (above 20 ml/100g/min) down to a severe hypotension of 40 mmHg. Autoregulatory ability however, was impaired after reinfusion (R) and despite an increase in MABP, the CBF was significantly reduced towards the critical value of 20 ml/100g/min. The non-autoregulating cats showed a CBF below critical value even in the face of a normal MABP of about 110 mmHg. C = Control.

The four cats which had fairly normal CBFs and EEGs up to 45 min after wounding despite a profound lowering of their MABPs to 38 mmHg tended to have lower ICPs and higher CPPs than the cats which could not maintain their CBF. Reinfusion of shed blood in all cats caused a severe increase in ICP and was associated with an even further decline in CBF.

CHEMICAL REGULATION OF CBF

1. CBF REACTIVITY TO CO_2 (GROUP V): All physiological data for this group including arterial blood gases are presented in Table V-A. All cats maintained a normoxic arterial PO_2 of 124-131 mmHg during both normocapnic and hypercapnic trials both before and after BMW. Hypercapnia (air + 5% CO_2) increased arterial PCO_2 from an average isocapnic state of 29 mmHg to about 54 mmHg before wounding and from 32 mmHg to 56 mmHg after wounding (Table V-A). Before wounding the blood pH decreased from 7.41 during normocapnia to 7.17 during the hypercapnic test ($[H^+]$ increased from 40 to 68 nmol/l) Thirty min after BMW the isocapnic pH was 7.29 (metabolic acidosis) which was reduced to 7.08 during hypercapnic trial ($[H^+]$ increased from 51 to 83 nmol/l).

Alterations in cranial and systemic pressures during the normocapnic state and hypercapnic tests both before and after BMW are illustrated in Fig V-A (upper bargraphs). As expected the ICP was increased from a pre-wounding value of 10 mmHg to about 39 mmHg, 30 min after BMW. The CPPs for corresponding periods were 127 and 72 mmHg. Pre- and post-wounding hypercapnic tests did not significantly change the levels of either MABP, ICP or CPP. The reactivity of CBF and CVR to hypercapnia before and after BMW is demonstrated in the bargraphs of Fig V-A.

The unwounded brain, showed a significant increase in CBF from 34 ml/100g/min to 72 ml/100g/min in response to the increased PCO_2 up to 54 mmHg. CVRs appropriately decreased from 3.77 to 1.95. Measurements in 3 cats revealed that all CBFs and CVRs returned to control values 40 min after cessation of the 5% CO_2 breathing: CBF was 36 ml/100g/min before hypercapnia and 34 ml/100g/min afterwards. After wounding, cats failed to show any changes in either CBF or CVR during the hypercapnic test (PCO_2 56 mmHg). Likewise all rCBFs thoughout the brain failed to respond to hypercapnia. (Fig V-B, Table V-B) Periwound tissues developed a 40% decrease in blood flow during the post-wounding hypercapnic trial (Fig V-B). While apparently large, this rCBF decrease was stastically not significant.

Because Koch et al (60) demonstrated that the effect of hypercapnia on CBF was almost completely abolished in cats after 12 minutes of total cerebral ischemia, we excluded data from 2/7 cats in which the rCBFs were very low 30 min after wounding just before the hypercapnic trial. Their prewounding CBF response to hypercapnia, however, was intact.

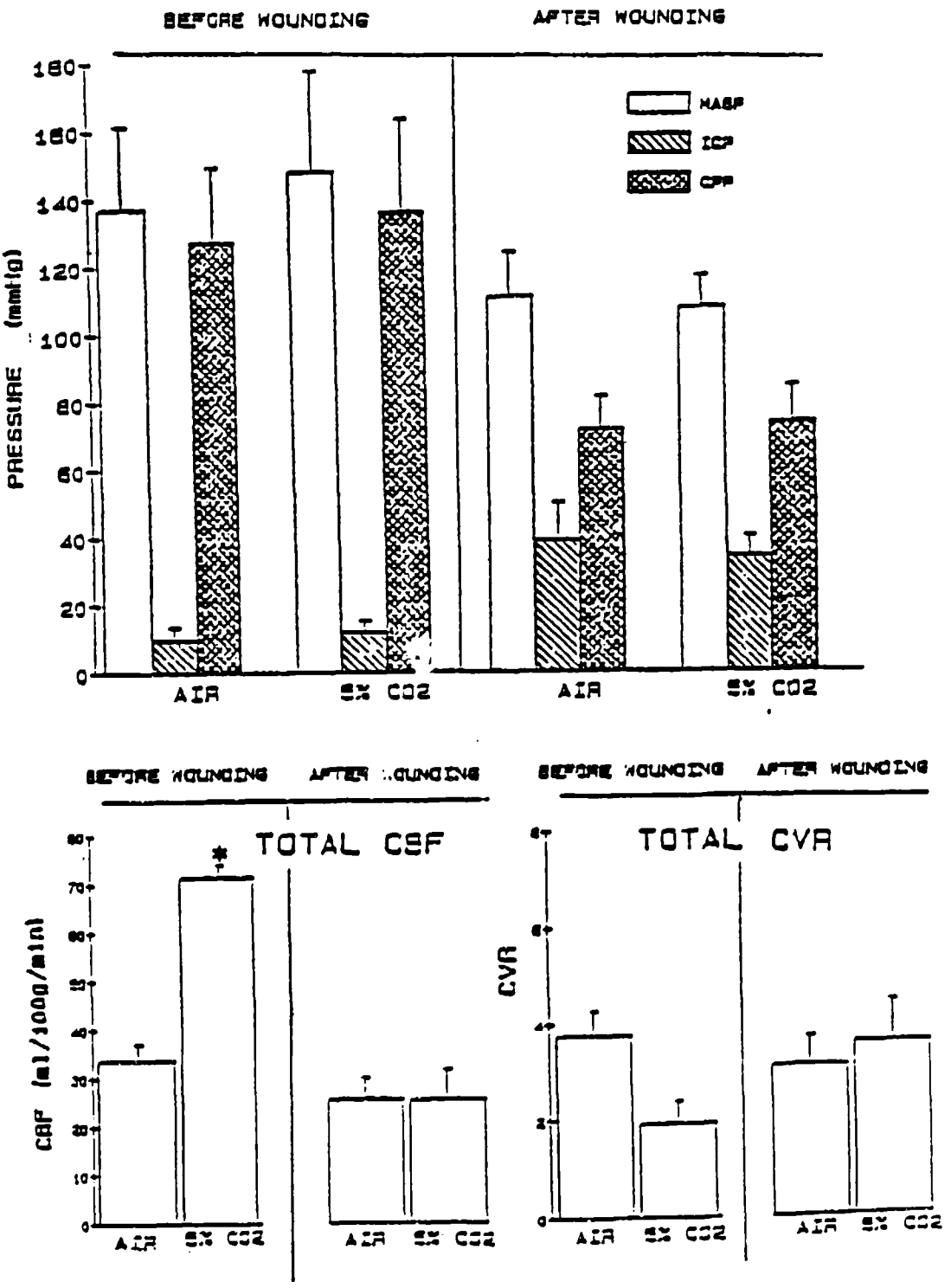

Fig V-A: Alterations in systemic and intracranial pressures and in total CBF and CVR before and after BMW in response to normoxic-isocapnic and hypercapnic breathing. The reactivity of CVR and CBF to hypercapnia was abolished after BMW. * Significant as compared to air breathing before/after wounding.

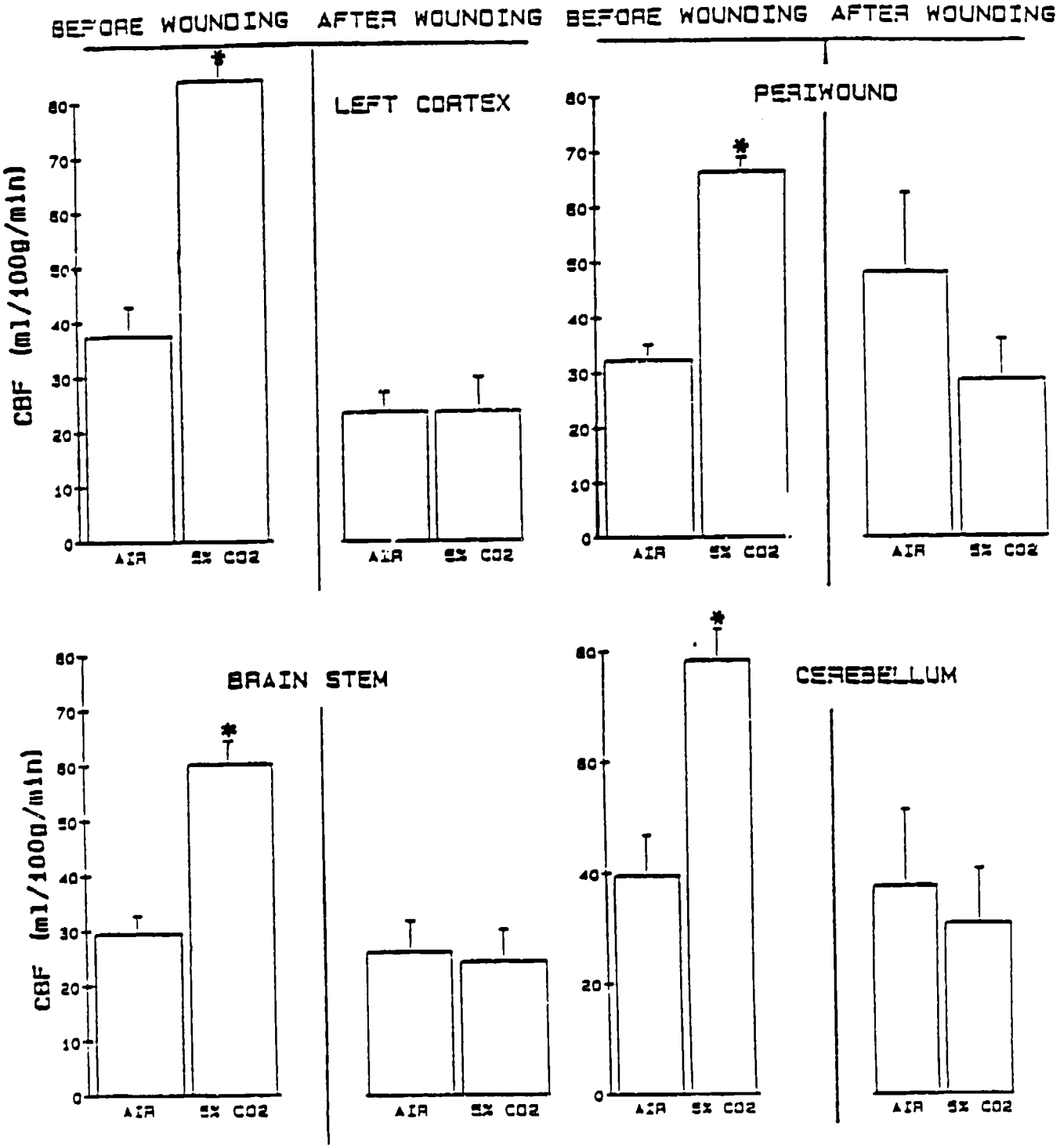

Fig V-B: Changes in rCBF of 4 selected structures before and after BMW in response to normoxic-isocapnic and hypercapnic breathing. The reactivity of rCBF to hypercapnia was entirely abolished in all brain structures and was even inversed in periwound tissues. * Significant as compared to air breathing before/after wounding.

CBF REACTIVITY TO HYPOXIA (GROUP VI): All physiological data for 4/7 cats in this group are provided in Table VI-A. Data from 3/7 cats which showed extreme reductions in CBF after wounding were excluded from analysis of the CBF response to hypoxia after wounding. Their pre-wounding reaction to hypoxia was normal and CBF data from 2 of these cats were used for evaluation of the normal CBF response to hypoxia.

The cats maintained a PCO_2 of 30-33 mmHg during both normoxic and hypoxic trials before and after BMW. The PO_2 during pre-wounding normoxia was 127 mmHg and dropped to 54 mmHg during hypoxia induced by breathing 10% O_2. After wounding the normoxic value of arterial PO_2 was 127 mmHg on average and dropped to 53 mmHg by breathing the same hypoxic mixture. The pH was not changed during the pre-wounding hypoxic trial, 7.39 versus 7.40 ($[H^+]$ 41 nmol/l) but it was reduced to 7.30 ($[H^+]$ 50 nmol/l) thirty minutes post-wounding and was 7.33 ($[H^+]$ 47 nmol) after the post-wounding hypoxic test.

The MABP both before and after BMW was slightly but not significantly increased (12%) during hypoxic tests. The pre-wounding ICP was 13 mmHg and was not changed by hypoxia. Thirty minutes after wounding the mean ICP was 60 mmHg which increased 14% during hypoxic trial. The mean CPPs after wounding were 79 mmHg during normoxia and 87 mmHg during the hypoxic trial.

The change in CBF and CVR to hypoxia before and after BMW is demonstrated in the lower bargraphs of Fig VI-A. Before wounding the cats developed significant increase (35%) in total CBF in response to 10% O_2 breathing (pO_2 = 54 mmHg); CBF rising from 33 ml/100g/min to 45 ml/100g/min. Though CVR tended to decrease, the decrease was not significant. The CBF, CVR, and rCBFs all returned to control levels 40 min after the pre-wounding hypoxic test (determined in 3/7 cats). Their mean total CBF was 29.1 ml/100g/min before the hypoxic test and 28.7 ml/100g/min afterward, indicating a complete recovery of CBF to pre-hypoxic values before BMW. After wounding all cats failed to show any change in total CBF or rCBFs during the hypoxic trial (PO_2 53 mmHg) (Fig VI-B). Total CVR failed to show even a tendency to decrease.

The responsiveness of all rCBFs to hypoxia before and after BMW is presented in Table VI-B. These data strongly suggest that BMW impairs the mechanisms of CBF increase to hypoxia throughout the brain. The periwound area may be particularly vulnerable to this impairment.

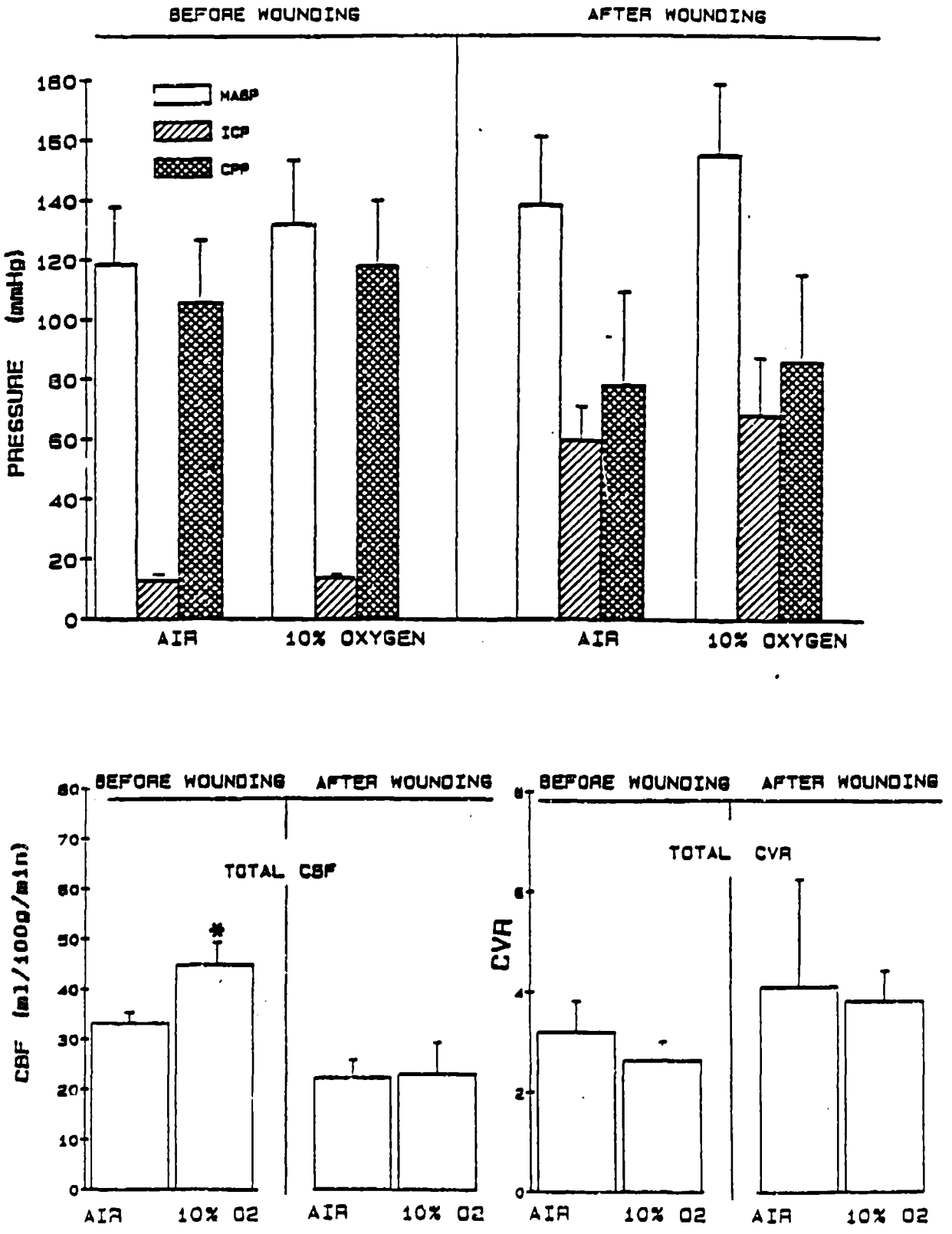

Fig VI-A: Alterations in systemic and intracranial pressures and in total CBF and CVR before and after BMW in response to normocapnic-normoxia and hypoxia. The reactivity of CVR and CBF to hypoxia was abolished after BMW. * Significant as compared to normoxic air breathing before/after wounding.

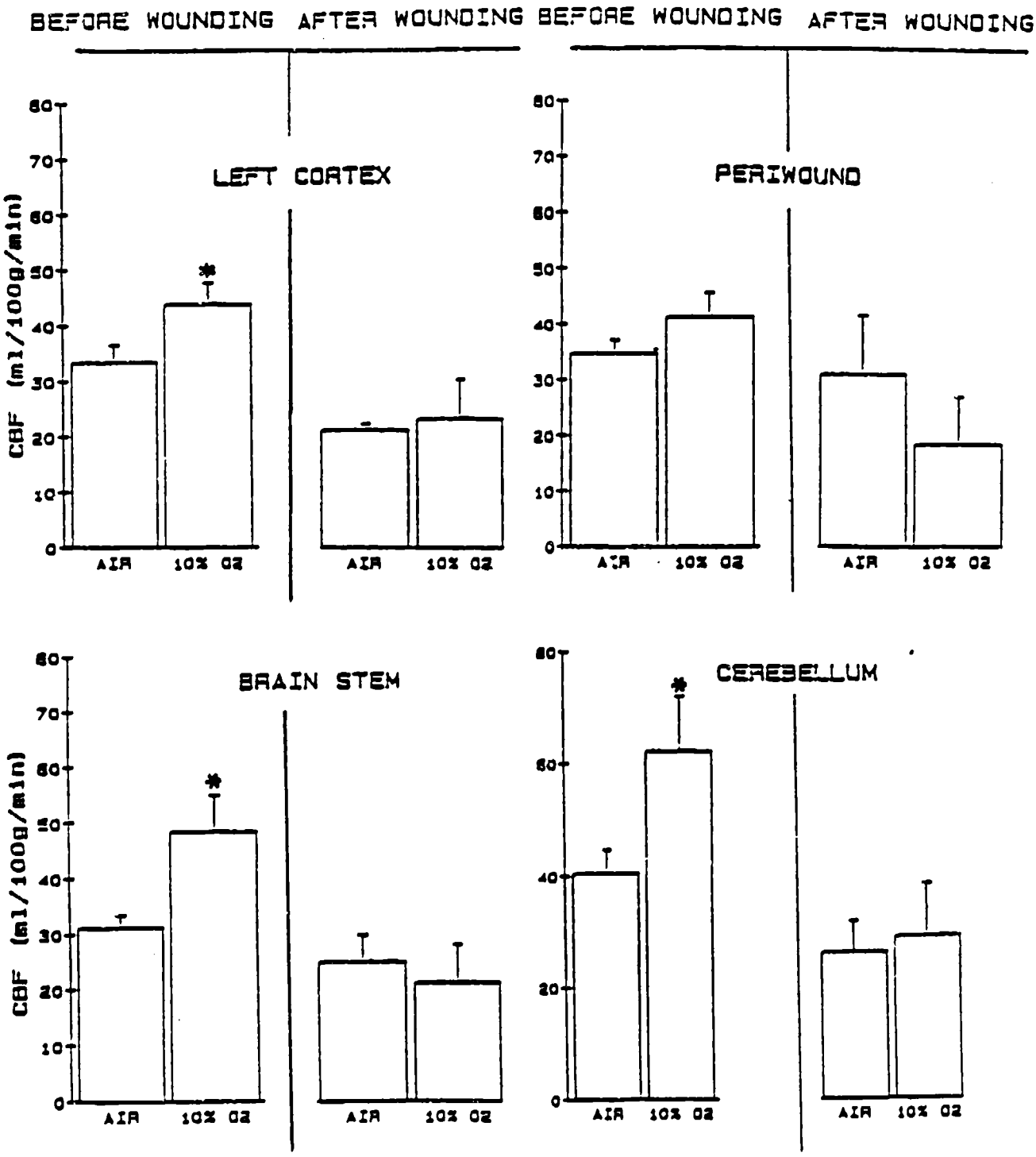

Fig VI-B: Changes in rCBF of 4 selected stuctures before and after BMW in response to normocapnic-normoxia and hypoxia. The reactivity of rCBF to hypoxia was entirely abolished in all brain stuctures and was inversed in periwound tissues.
* Significant as compared to air breathing before/after wounding.

OTHER EFFECTS OF BRAIN WOUNDING

CHANGES IN ECG: Bradycardia and cardiac arrhythmias developed simultaneously with BMW, (Fig 1). Post-wounding ECG abnormalities in these ventilated cats persisted only for 5 to 10 min before returning to a normal sinus rhythm (Fig 2). No ECG abnormalities were observed in normotensive and hypotensive unwounded cats.

CHANGES IN BGC AND HEMATOCRIT: BGC and HCT values for groups I to IV are shown in Tables I-A to IV-A. No significant changes in these variables occurred in unwounded, control cats or in wounded, normotensive animals during the 100 min experiment. Unwounded, hypotensive cats showed significant increases in BGC only after moderate and severe hypotension (MABP 68-48 mmHg) 20 and 45 min after injury; HTC remained unchanged during hypotension. Wounded, hypotensive cats demonstrated a significant increase in BGC starting 5 minutes post-wounding. HCT was significantly reduced only following severe hypotension, 45 minutes post-wounding.

CHANGES IN ORGAN BLOOD FLOW (OBF): Mean values of blood flows in heart muscle, skeletal muscle, spleen, renal cortex and medulla separately, adrenals (cortex and medulla together), and spinal cord during 5 consecutive measurements in groups I to IV are presented in Tables I-C to IV-C. Selected normalized data are presented in Figures 8 to 11.

In unwounded normotensive cats (group I), OBFs showed no significant changes during the entire period of experiment (Table I-C and Fig 8).

In wounded normotensive cats (group II), cardiac blood flow increased 62% 5 minutes after BMW and then returned to control levels thereafter. All other OBFs became moderately decreased after wounding but the observed flow reductions were not statistically significant.

Hypotensive unwounded cats (group III), showed 30% reduction in cardiac blood flow when MABP was reduced from 116 mmHg to 89 mmHg, 5 min after bleeding started. Cardiac blood flow then increased to normal levels with moderate and severe hypotension. It was slightly but not significantly increased after blood reinfusion. This suggestive reduction of cardiac blood flow with hemorrhage contrasted with the 62% increase in cardiac blood flow in the wounded, normotensive cats. Spleen blood flow in this hypotensive group was significantly reduced (-75 to -89%) during all three levels of hypotension but recovered after reinfusion (Table III-C). Blood flow in the cortex and medulla of the kidney and the adrenals showed different degrees of reduction at various levels of hypotension. Renal blood flow reductions were significant 45 minutes after hemorrhage began. Cervical spinal cord blood flow remained at control levels during the entire hypotensive trial indicating intact spinal blood flow autoregulation as in the brain (Fig 10). Unwounded hypotensive cats showed a complete recovery of blood flow in all investigated organs after reinfusion. There was an increase of 31% in spinal cord blood flow with blood reinfusion, (Fig 10) but this increase was not statistically significant.

Wounded hypotensive cats (group IV), demonstrated a similar pattern of organ blood flow as the unwounded hypotensive cats (compare Tables III-C and

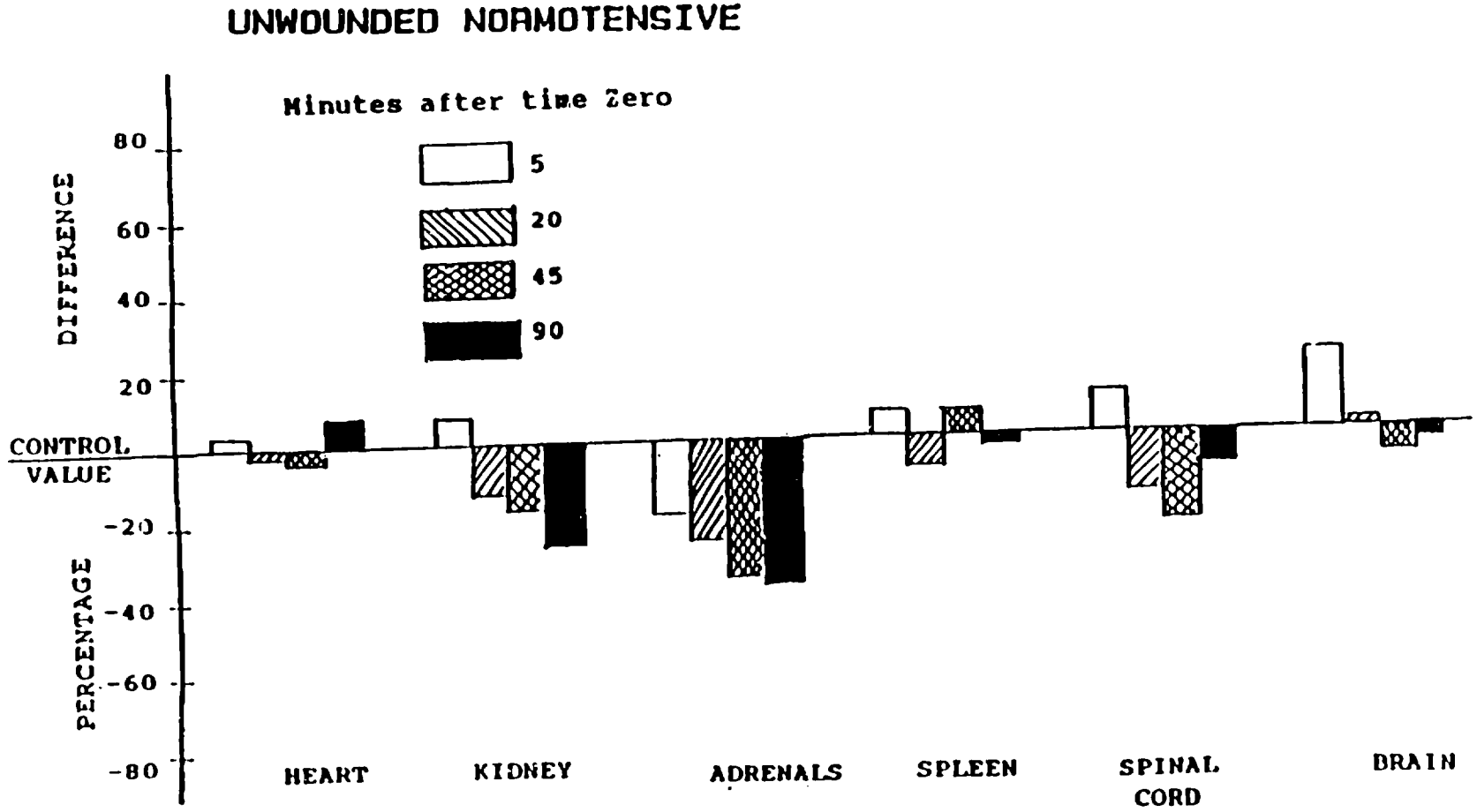

Fig 8: Alterations in mean organ blood flows and total CBF during a 100 minute period in unwounded control cats. This experimentation period corresponds to the times before wounding/bleeding (-10 min, base line) and at 5, 20, 45, and 90 min afterward. * Significant as compared to base line control values; $p>0.05$; $n=7$.

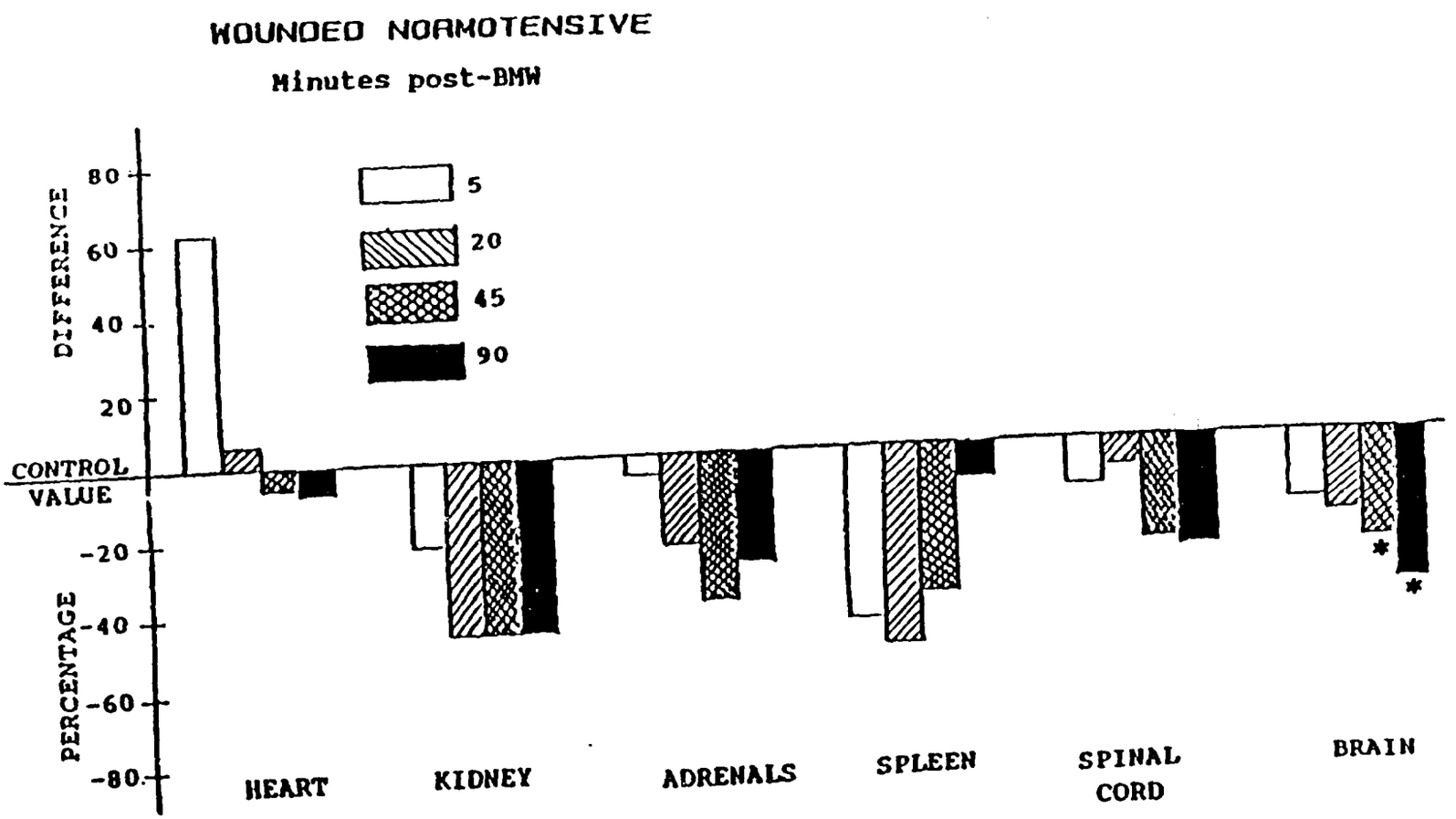

Fig 9: Alterations in mean organ blood flows and total CBF at 5, 20, 45, and 90 min after BMW in normotensive cats. Significant and extreme reductions in OBFs and CBF resembles a state of shock after BMW. * Significant as compared to pre-wounding control value ; $p>0.05$; $n=7$.

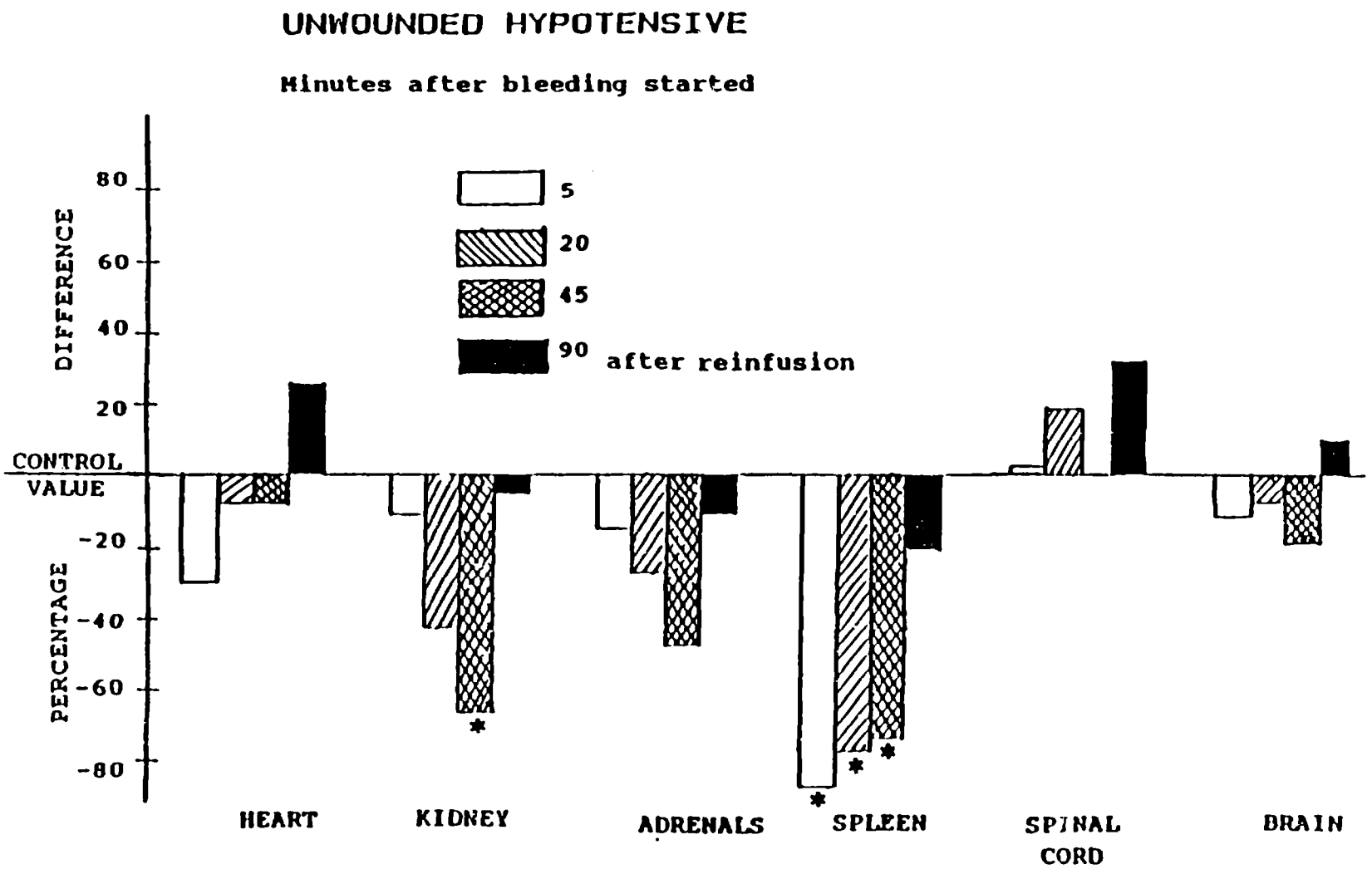

Fig 10: Alterations in mean organ blood flows and total CBF at 5, 20, 45 min after bleeding started in unwounded hypotensive cats and after reinfusion at 90 min. Brain and spinal cord maintained their blood flows at 3 levels of hypotension. Blood flows in all organs returned to their pre-hypotensive levels after reinfusion.

* Significant as compared to normotensive control values, $p<0.05$; $n=7$.

IV-C). Flow reductions became significantly reduced in kidney, adrenals and spleen. Cardiac blood flow, unlike that in wounded normotensive cats, was not increased after wounding and HH. Likewise, it did not show as much of a decrease as after HH in unwounded cats. Factors tending to increase cardiac blood flow with brain wounding appeared to counter weigh those causing cardiac flow reductions with HH. The extreme reduction in CBF, after reinfusion, when other organs generally regained normal blood flows was, outstanding (Fig 11).

These changes in OBF and CBF are summarized below:

	Heart	Kidney	Adrenals	Spleen	Spinal	Brain
Group I (unwounded)	no △	no △	no △	no △	no △	no △
Group II (wounded normotensive)	↑ @ 5′	red	red	red	red	sig ↓ @ 45′
Group III (unwounded hypotensive)	↓ @ 5′	sig ↓ @ 45′	red	sig ↓ @ 5′	↑ @ 20	no △
Group IV (wounded hypotensive)	sl ↑ @ 5′	sig ↓ @ 45′	sig ↓ @ 45′	sig ↓ @ 5′	no △	sig ↓ @ 5′ no ↑ w/ reper-fusion

sig = statistically significant
red = reduction

↑ = increase
↓ = decrease

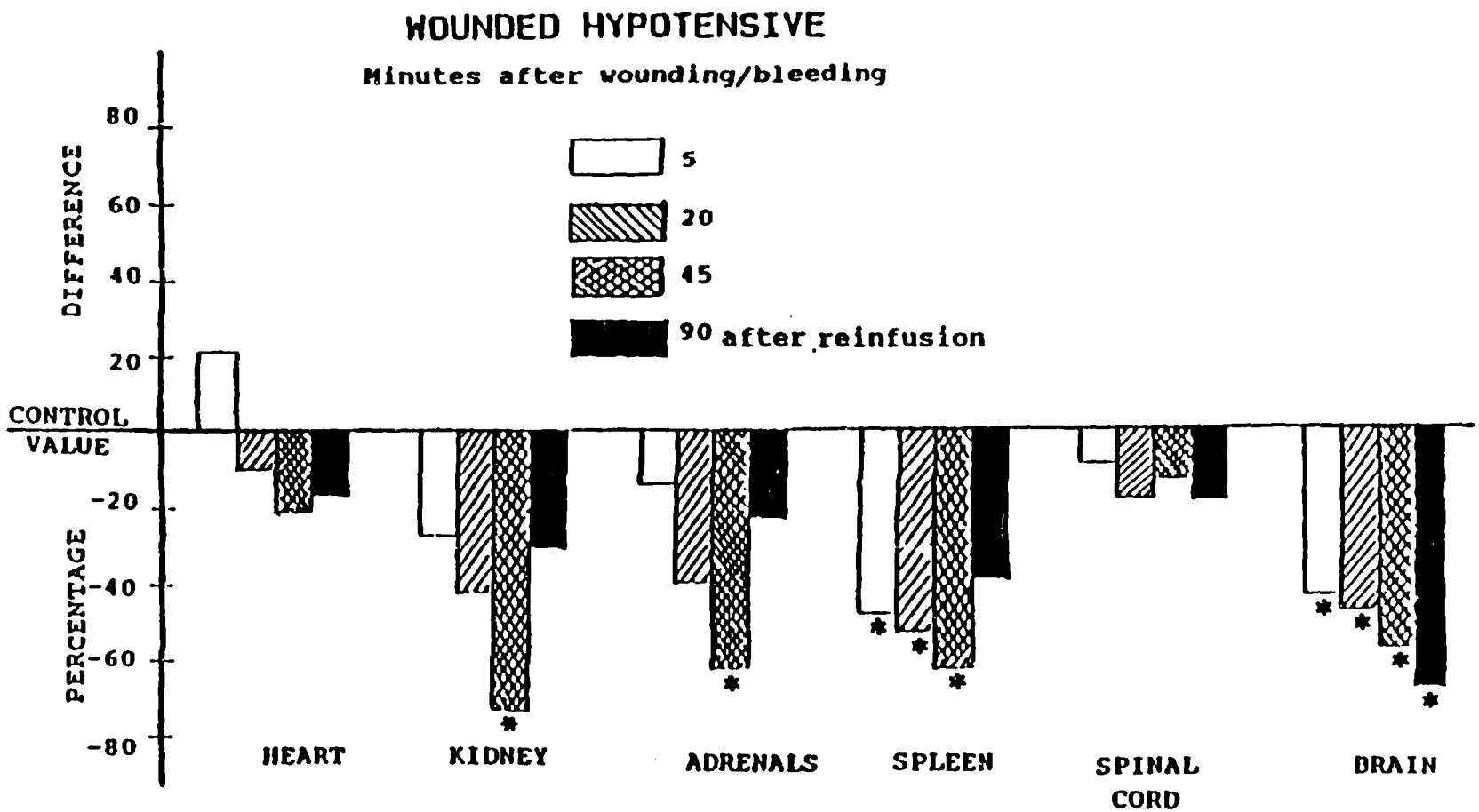

Fig 11: Alterations in mean organ blood flows and total CBF at 5, 20, 45 min after wounding/bleeding at 3 hypotensive levels and after reinfusion at 90 min. Association of wounding and hemorrhagic hypotension produced significant and extreme reductions in OBF and CBF resembling a state of shock. Although OBFs were largley improved after reinfusion the decrease in total CBF was contiued. * Significant as compared to pre-wounding/bleeding control values; $p>0.05$; $n=10$.

DISCUSSION

The experiments which we have undertaken, studying the effect of brain wounding on mechanical and chemical regulation of CBF, have never been done before. They represent, however, a direct continuation of the line of thought which has sought to examine the effect of other pathophysiological states (e.g. increased ICP, hypotension or fluid percussion injury) on CBF regulation. While one might argue by analogy from these paradigms to a missile wound of the brain, such a direct transfer of concepts concerning CBF regulation might produce erroneous conclusions because none of the usual experiments studying disturbances in CBF regulation mimic even closely an actual brain wound caused by a missile. Brain wounding by a missile is a complex phenomenon involving focal injury, and physiologic effects best attributed to brain stem dysfunction plus acute and chronic increases in intracranial pressure affecting the brain in general. Each of these components of missile wounding might affect CBF regulation differently either locally or widely throughout the brain. We undertook these experiments, therefore, to examine mechanical and chemical CBF regulation after an actual missile wound to the brain; to examine directly the dysfunction incurred rather than to reason by analogy or to speculate upon possible effects based on non- pertinant prior experimentation.

CHANGES IN CBF AND OTHER PHYSIOLOGIC VARIABLES IN CONTROL CATS; GROUP I

Unwounded, normotensive cats (N=7) showed no significant changes in total CBF, CVR, rCBFs, MABP, ICP, CPP, blood gases, pH, HCT and BGC throughout the entire 100 min experiment (Tables I-A and I-B). Likewise, EEG and ECG were normal. All control rCBFs measured in our experiments were in the feline range reported by other investigators, using various methods including the microspheres technique (2,23,38,54,76,77,81,87,124,141). Regional rCBF measurements in these cats showed no left/right hemisphere differences, (Figs IA,B). Thus, our laboratory technique appears to provide reliable CBFs.

CHANGES IN CBF AND OTHER PHYSIOLOGIC VARIABLES IN WOUNDED, NORMOTENSIVE CATS; GROUP II

Total CBF in wounded, normotensive cats (N=7) gradually decreased during the 90 minute post-wounding period (Figs II A,B; Table II-B). Regional CBFs showed some variability indicating that the reduction in blood flow was not uniform throughout the brain. Cortical structures and caudate nuclei showed the highest reduction in blood flow at 20 min post-wounding while brain stem structures showed no significant flow reductions for at least the first 20-45 min after injury. The longer standing, post-wounding elevated mean ICP in these BMW cats approximated 40 mmHg and the observed CBF patterns (reduced cortical and retained brain stem flows) resembled those obtained by Zierski (141) who elevated cats' ICPs up to 40 to 60 mmHg by means of a supratentorial, epidural balloon. The post-wounding mean ICP in our study approximated 60-40 mmHg. Therefore, the observed rCBF pattern (reduced cortical and retained brain stem flows) may be partly related to post-wounding elevations in ICP. It has been postulated that when ICP increases enough to reduce CBF, a redistribution in rCBF occurs favoring the brain stem. By this means neurons in the medullary vasomotor centers which control

circulation remain most protected from ischemia. (141)

The periwound area showed no reduction in rCBF for the first 45 min after BMW as compared to reduced rCBF in other cortical structures (Fig II-B). For example, left cortical structures in the aggregate showed a 29% decrease in their blood flow 20 min after BMW, as compared to only 1% reduction in periwound blood flow. The relative hyperperfusion about the missile track may be explained by the effects of wounding on precapillary resistance vessels. We may hypothesize that wounding with crushing and laceration of tissues resulted in local tissue effects as: local acidosis or release of vasoactive substances as adenosine (139), prostaglandins (29,63,84,118,119) and catecholamines (27,28) which might have dilated the periwound blood vessels and maintained local CBF about the wound track (6,22,129,134).

Transient hyperemia of damaged muscle has been reported following a high velocity missile wound to the leg in the dog (112). It was hypothetized that pressure waves associated with missile transit inhibited sympathetic vasoconstrictor discharges and caused hyperemia in muscles adjacent to the missile track. Sympathetic stimulation apparently does not change CBF in normal cats (12,48) even though it may decrease the diameter of large pial arteries (4,12). While evidence exists for neural regulation of feline CBF during acute systemic hyper and hypotension (38), it is unknown whether sympathetic control of CBF is affected by BMW.

Possible effects of reduced MABP, increased ICP or reduced CPP on CBF

These brain wounded, normotensive cats demonstrated significant reductions in total and regional CBF 45 minutes after wounding despite mean MABPs of 90-100 mmHg, ICPs of ~40 mmHg and CPPs of 70-80 mmHg. In cats without brain damage adequate CBF can be maintained following hemorrhagic hypotension with MABPs as low as 30 mmHg, with ICPs as high as 70-100 mmHg or with CPP reduced to 30-40 mmHg (40-43,69,70,89,141,144). Our data suggest that following BMW the level of ICP elevation (or CPP reduction) which affects CBF is reduced. In other words, relative to CBF maintenance, the missile-injured brain is much more sensitive to elevations in ICP or reductions in CPP than the normal brain. We interpret the decrease in CBF in our cats, despite an apparently adequate ICP and CPP, as one evidence of failure of CBF autoregulation mechanisms after brain wounding. With the post wounding ICP elevations which occurred in these cats they would have had to decrease their CVRs to maintain CBF. Five minutes after wounding their total CVRs tended to show a decrease in response to the ICP elevation (CPP reduction); after that, however, CVRs inappropriately increased leading to loss of CBF. Thus, it appears that in normotensive brain-wounded cats some appropriate attempt to alter CVR was made for the first several post-wounding minutes in order to maintain normal CBF. After that these mechanisms appeared to fail and CBF fell.

Although CBF decreased in these cats, residual flow was usually greater than 20 ml/100 gm/min, sufficient to prevent cerebral edema (56,122) or brain energy failure (3,123,143,144). Thus, neither of these mechanisms can be impuned for the inability of the missile-wounded brain to regulate its blood flow. We may, however, speculate on possible other mechanisms.

Possible effects of vasoactive substances on CBF

Various vasoactive substances may be released into the brain parenchyma, cerebrospinal fluid (CSF) or blood after CNS trauma (26,27,50,82,92,101,125,134).

For instance, our previous experiments have demonstrated extremely high levels of the prostoglandins TxB2, $PGF_{1\alpha}$, PGD_2, and PGE_2 in the CSF within minutes of wounding (113). Mediators in CSF could affect blood vessels widely throughout the brain.

The hyperemia (absolute or relative) which we have observed about the wound track or in contracoup areas of the brain (see prior yearly report) also might be produced by vasodilatory substances as adenosine, histamine, GABA, and PG-$F_{1\alpha}$ from tissues. (39,71)

Disruption of the blood- brain barrier (BBB) about the wound track (32) may cause leakage of the vasoactive materials as serotonin, prostoglandins, and neuropeptides (26,27,82) from the blood into the brain extracellular space particularly near the missile track. Such substances could also affect brain blood vessels. Brain missile wounding (this report) and ICP elevations (110) have been shown to release substantial amounts of norepinephrine in the blood. Although these catecholamines normally act as vasoconstrictors, norepinephrine has been shown to act as vasodilator after it penetrates the BBB (32,44,96). Dopamine exerts a dual vasoconstrictive and vasodilatory effect on brain vessels which is dependent on its plasma concentration (28). Thus, plasma catecholamines acting on cerebral blood vessels adjacent to the wound track could also be a factor in late post-wounding CVR changes and CBF reduction. Observed blood flow changes occurred several minutes after wounding. Possibly, this delay may be related to the time required for vasoactive substances to reach the operative CBF resistance vessels or the time needed for chemical reactions to occur about the reacting blood vessels.

The progressive increase in CVR leading to decreased CBF and loss of CBF regulation following brain wounding deserves further investigation because controlling post wounding CVR and blood flow regulation will allow the most optimal post-wounding CBF to be maintained.

CHANGES IN rCBF AND OTHER PHYSIOLOGIC VARIABLES IN UNWOUNDED CATS SUSTAINING HEMORRHAGIC HYPOTENSION; (GROUP III)

Normally, cerebral vessels dilate with HH (4,12,21,33,120,121). CVR decreases when MABP falls and CBF is maintained: the brain "autoregulates" its own blood flow (mechanical autoregulation). Unwounded cats (N=8) in our experiments uniformly demonstrated intact total CBF autoregulatory mechanisms following withdrawal of blood, at least down to a MABP of 40mmHg and a CPP of 30mmHg; as MABP fell CVRs decreased and CBF was maintained. While whole brain CBF remained intact, (Fig III-A) cortical areas tended to show some decrease in rCBF, (Fig III-P). Brain stem rCBFs, however, were maintained, (Fig III-B) again indicating a redistribution of blood flow towards brain centers intimately involved with cardiovascular control. The preservation of CBF autoregulation down to a MABP of 40 mmHg in these cats is consistent with data reported for cats and other mammals subjected to HH (15,34,35,72,80,88,100,120,121). Possible local chemcial regulators

effecting CVR during HH may be increases in $[H^+]$ and adenosine (8,9,67,74,133,139).

Hemorrhagic hypotension characteristically produces arterial acidosis (64,121) and the normocapnic cats in this experimental group showed this effect: pH fell from a control of 7.39 to 7.21 (H+ increased from 41 to 63 nmol/l). This level of acidosis continued after blood reinfusion which restored MABP, CPP, and CVR to normal. CBF remained normal even 90 minutes after HH and subsequent reinfusion despite this prolonged metabolic acidosis.

Neither CSF nor tissue pH was measured in these experiments but in any case our data clearly indicate that cerebral autoregulatory mechanisms were not adversely affected by arterial metabolic acidosis either during the period of HH or afterwards during blood reinfusion. Likewise, CBF was not affected with reinfusion of shed blood which might have contained mediators released into the blood by the HH.

CHANGES IN rCBF AND OTHER PHYSIOLOGIC VARIABLES IN WOUNDED CATS SUSTAINING POST WOUNDING HYPOTENSION (GROUP IV)

Consideration of Table 1 (p 36) indicates that 5 minutes after wounding the mean ICP in the six cats that completely failed to maintain CBF with a falling MABP was almost twice that of the four cats which preserved CBF despite a decreasing MABP. At this time the post wounding CPP in cats maintaining CBF cats was 58 mmHg, in the range where one would have expected CBF autoregulation to occur, while the corresponding CPP for cats with greatly diminished CBF was 39 mmHg, a level where CBF autoregulation might be expected to fail (32,121,141-143). Cats maintaining CBF had CPPs greater than their ICP; while cats failing to preserve blood flow had ICPs greater than CPPs. Interestingly, however, 45 minutes after wounding the CPPs in autoregulating cats was 22 mmHg, considerably less than the 39 mmHg CPP seen 5 minutes after wounding in the non-autoregulating ones. This tends to confirm prior observations that the rate of decrease in CPP following wounding may be a critical factor in loss of CBF autoregulatory control (69,141). A more gradual reduction in CPP may be better tolerated; CVR mechanisms may be properly adjusted under such circumstances and CBF better maintained. The above implicates CPP reduction or, perhaps more properly, the rate of CPP reduction as a prime factor in the loss of CBF autoregulation following brain wounding and simultaneous hemorrhagic hypotension.

Reasons for post wounding increased in ICP (reduction in CPP)

The reason why some cats in our experiments developed higher ICPs (and lower CPPs) than others following brain wounds made by missiles of equal energy is unclear but the random occurrence of intracranial blood clots and an/or abrupt increase in cerebral blood volume (CBV) may be suspect. Grubb et al (41) studied the effects of increased ICP on CBV and CBF in monkeys. When ICP was raised to 70 mmHg (CPP of 40 mmHg) by infusion of mock CSF into the cisterna magna, CBV increased but CBF remained unchanged. With a further increase in ICP to 94 mmHg, CBV remained elevated and CBF declined significantly probably because compensatory mechanisms to accommodate increased intracranial volume had been used up. Measurement of intracranial blood clot volume after wounding is difficult, but measurement of CBV alterations after BMW will be pursued because knowing post wounding CBV will

directly influence recommendations concerning post wounding fluid/blood replacement therapy.

It is hard to impune the rapid occurrence of brain edema within a few minutes of wounding to account for the rapid rise in post wounding ICP. This possibility, however, must at least be considered. Another cause for CBF reduction would be venous outflow obstruction from cortical veins draining into the saggital sinus. (88,131) Perhaps animals with higher ICPs would be more subject to this complication. If so, the ICP rise from whatever cause would be the primary event; the venous outflow obstruction secondary.

Changes in post wounding CVR

Failure of cerebrovascular resistance mechanisms to adjust may also be a factor in CBF reduction in the six cats which failed to preserve CBF following BMW and HH because, theoretically, CBF could be maintained despite ICP increases (CPP decreases) if only the CVR could concomitantly decrease enough. We may only speculate upon mechanisms which might prevent appropriate CVR decreases following BMW and simultaneous HH.

As discussed, a widespread impairment of local tissue agents as adenosine following BMW might prevent needed vasodilatio..

A sympathico-adrenal discharge accompanies both HH (35,64) and BMW (see this report). A normal discharge in susceptible cats or a particularly strong sympathico-adrenal discharge in otherwise normal cats might have activated cerebral vasoconstrictor mechanisms and prevented CVR decreases in response to post-wounding ICP increases (CPP reductions). This could have lead to a loss of CBF in some of the cats. Activation of the sympathico-adrenal system has been postulated to be an important adjuvant factor in the development of vasospasm and brain ischemia during hemorrhagic shock (35,64). Pearce and D'Alecy (100) studied the cerebrovascular responses to a 20% volume hemorrhage in dogs and found that sympathetic vasoconstriction accounted for up to 20% of the post-hemorrhagic change in CVR. Fitch et al (34) observed that, in baboons, CBF autoregulation failed at higher MABP levels (60 mmHg) following HH than after drug-induced hypotension (40 mmHg). They postulated that HH activated the sympathoadrenal system which, in turn, caused constriction of the extraparenchymal cerebral blood vessels. This resulted in failure of CVR regulatory mechanism and the failure of CBF autoregulation at the higher MABP level.

Additionally, the function of endothelial cells as "mechanotransducers" may be also altered because of direct wound damage or flow-related forces (22). This would alter their responsiveness to decreasing MABP or CPP.

Whether cats subject to BMW and simultaneous HH would autoregulate as MABP was reduced was evident within 5 minutes of wounding (Figs 6 and 7). The amount of blood loss during this period averaged 49 ml for both the autoregulating and non-autoregulating cats. Furthermore, those cats that maintained CBF to decreasing MABP did so in the face of considerably greater blood loss than 49 ml as these animals were continually bled for 45 minutes after brain wounding. Thus, blood loss per se seems not to be a major factor in the abolition of CBF autoregulation.

Whether one could demonstrate increased $[H^+]$, adenosine, or other putative agents in cats that could maintain their CBF following brain wounding and HH and a lack of this agent(s) for cats that could not maintain CBF would be of importance for future research in order to determine the underlying biochemical mechanisms for this bimodel response following wounding and HH. This knowledge might suggest appropriate treatments to maintain CBF autoregulation.

REPERFUSION FAILURE

Perusal of Table 1 and Figs IVA, 7 and 8 indicates that reinfusing shed blood into the brain-wounded hypotensive cats did not restore CBF whether the cats did or did not maintain CBF following BMW and HH. Other investigators have also demonstrated that once a reduction of CBF has occurred owing to MABP decrease from either ICP increase or hemorrhagic hypotension, it has proven difficult to restore CBF again by raising the MABP with blood or fluid replacement. For instance, Slater et al (121) measured sequential changes in rCBFs in dogs during the course of graded hypotension down to 50 mmHg. Paradoxically, following reinfusion of shed blood, which restored MABP, CBF fell. Lewelt (76) subjected fluid-percussion-injured cats to severe HH and observed that their CBFs fell from control levels, 37 ml/100g/min, down to 9 to 18 ml/100g/min indicating autoregulation failure. Subsequent reinfusion of shed blood raised the MABP to pre hemorrhage levels but was associated with a further decrease in CBF. Poole's group (103,104) induced hemorrhagic hypotension (MABP 40 mmHg) for 30 minutes in dogs. CBF fell about 20%. They restored blood volume and MABP by reinfusing either lactated Ringer's solution or 6% hetastarch but neither fluid restored CBF to control levels. Similar results were obtained in dogs whose MABPs were lowered to only 55 mmHg by bleeding after ICP had been elevated to 30 mmHg for 5 minutes by means of an epidural balloon. It was hypothesized that autoregulatory loss, increased cerebrovascular resistance, or both accounted for the failure of fluid resuscitation to restore CBF.

Reinfusion failure in our experiments of brain wounding and hemorrhagic hypotension might possibly be explained by the "no reflow" phenomenon which has been extensively studied in the context of cerebrovascular disease and cerebral ischemia. The initial observations of Ames (1) showed that once blood flow was reestablished to ischemic brain, large perfusion defects persisted. Subsequent studies have demonstrated that such permanent ischemic lesions develop in a diphasic fashion. Hossmann (56) commented that following a major arterial occlusion there was an acute fall in CBF of about 70%. After 4 hours of continued occlusion the flow reduction became even greater. The secondary CBF decline appeared to correlate with a progressive brain swelling called ischemic or "cytotoxic" edema. With cytotoxic edema, fluid is taken up within brain cells. It has been shown that a fluid shift from the extracellular to the intracellular compartment occurs with a CBF as high as 30 ml/100gm/min indicating that even at this high flow there is an initial change in cellular ionic homeostasis mechanisms. No net gain of water occurs within the brain at this stage. For cats, the CBF threshold for development of cytotoxic brain edema is about 10-15 ml/100g/min (55). When

CBF falls to this level plasma water crosses the BBB into the extracellular space. Fluid from the extracellular space, in turn, continues to accumulate intracellularly. Swollen astrocytes compress brain capillaries, increase cerebrovascular resistance, and decrease or prevent rCBF. At a CBF of 10 ml/100gm/min or less homeostatic mechanisms maintaining cellular membrane ionic pumping mechanisms completely fail and cell death occurs. After several hours of ischemic, cytotoxic edema the BBB may break down and plasma fluid and constituents then enter the brain. At this point "vasogenic" edema is superimposed upon "cytotoxic" edema over the entire brain.

Once brain ischemia occurs, autoregulatory control mechanisms may be impaired. Elevations in systemic arterial pressure then cause concomitant increases in ICP. This may prevent an effective CPP increase or even reduce CPP leading to a decreased CBF.

We hypothesize that reperfusion failure in our non-autoregulating cats occurred because the rapid CPP and CBF reductions in these animals led to the onset of generalized cytotoxic edema over the entire brain and capillary narrowing. Such cytotoxic edema would be in addition to the slight vasogenic edema which develops early around the wound track. Because autoregulation had clearly failed in these animals, blood reinfusion elevated both MABP and ICP equivalently resulting in only a slight improvement in CPP, Fig 6. Thus, not only was CPP low in these animals but brain capillary resistance was high. Both mechanisms tended to prevent reinfusion. Once CBF had declined to the 10ml/100g/min range or less these animals were doomed owing to severe ischemia and failure of cellular metabolic processes within the brain.

Reperfusion failure in the autoregulating group of 4 cats is less easily explained. In these animals CBF was maintained in the 20 to 25 ml/100g/min range despite severe reductions in MABP to 40 mmHg, and CPP to 25 mmHg. These cats exhibited some autoregulation of CBF when MABP was decreasing and decreased their CVRs with falling MABP. Though their CBFs remained above the threshold level required for cytotoxic edema formation, 10-15 ml/100g/min, their CPPs were reduced considerably below 40mmHg. As with the non-autoregulating group, ICP rose in these cats when reinfusion restored MABP. This ICP response to increasing blood pressure indicates loss of autoregulatory control as demonstrated by Langiftt and Miller (89). It thus appears that this autoregulating group of animals could maintain CBF when MABP decreased but could not regulate CBF when challenged by an increasing MABP. Their ability to mechanically autoregulate CBF was therefore incomplete. Hence, in these cats when blood reinfusion elevated MABP the vascular pressure was immediately transmitted into the intracranial space, which raised ICP, lowered CPP and reduced CBF (Figs 6 and 7). Miller et al (89) observed a similar phenomenon in their experiments studying CBF regulation during experimental brain compression: with autoregulatory breakdown CBF fell despite a rising CPP. They termed maintance of CBF with rising CPP after autoregulation failure "false autoregulation". It is tempting to hypothesize that these cats which maintained CBF with decreasing MABP did not have early cytotoxic edema formation, massive autonomic activity increasing CVR, or inhibition of local chemical mediators during the 45 minute period when MABP was being reduced. After reinfusion, however, total CVR rose to extremely high levels (Fig IV-A). Whether this was from massive movement of water into the brain, simultaneous sympathetic discharge causing cerebral vasoconstriction, extreme stasis of blood within cerebral capillaries or cortical venous outflow obstruction is unknown.

It would be instructive to determine the cerebral blood volumes (CBV) and brain water content in similar reperfused animals. If the CBV remained decreased following reperfusion, this would suggest that there was a lowered capillary volume. This could come about by the effects of cytotoxic edema or from autonomic activity and cerebral vasoconstriction. If brain water were increased cytotoxic edema would be suspect. If CBV were increased it would suggest that there was pooling of blood within the brain and it was vascular stasis which prevented adequate reperfusion. Knowing the cerebral blood volume in BMW-HH animals would be important relative to determining mechanisms of reperfusion failure and in directing treatment. For instance, if the CBV were increased, increasing the blood volume further to try and improve CBF might further exacerbate the cerebral circulatory dysfunction. If the cerebral blood volume were small perhaps volume expansion would improve CBF. Other therapies to improve CBF would have to be directed at reducing cytotoxic or vasogenic brain edema or the possible cerebrovascular autonomic dysfunction.

Rheological Factors

Rheological factors as intravascular erythrocyte sludging and increased blood viscosity or direct damage to vascular endothelial cells could also play a role in reperfusion failure (22,36,51). Fujimoto et al (36), studied intravascular platelet aggregation after acute intracranial hypertension by epidural balloon compression in cats. They suggested that platelet aggregates and decreased capillary deformability which impeeded red blood cells disturbed the brain's microcirculation. Kim and Sano (59) reported that activation of platelets, as well as morphological changes of platelets and erythrocytes may contribute to the occurrence of a no-reflow phenomenon following cerebral ischemia induced by either raised cisterna magna pressure or lowered MABP.

A HIGH PRIORITY SHOULD BE GIVEN TO STUDIES TO 1) DETERMINE THRESHOLD CONDITIONS LEADING TO RECIRCULATORY FAILURE IN THE BRAIN; 2) MECHANISMS UNDERLYING THIS FAILURE AND 3) EVALUATE METHODS FOR REESTABLISHING REPERFUSION TO THE WOUNDED, ISCHEMIC BRAIN.

REACTITIVITY TO HYPERCAPNIA AND HYPOXIA

Arterial PCO_2 and PO_2 both affect CVR mechanisms. CBF increases in response to hypercapnia and conversely decreases in response to hypocapnia (7,46,58,98,99,140). Vascular reactivity to CO_2 is the more sensitive mechanism than reactivity to O_2 so even slight variations in PCO_2, on the order of 5 to 10 mmHg, are reflected in rapid changes of CBF (20-30 sec for pial vessels) (132). Arterial PO_2, on the other hand, must be reduced to approximately 50 mmHg, before effecting a CBF increase (58,83,91). It has been concluded that the vasodilatory effect of hypercapnia is related to increased arterial PCO_2 itself, rather than the associated decrease in arterial pH (7,74). CO_2, (unlike H^+) can freely penetrate into the cerebral extracellular space, dissociate there, alter the extracellular and perivascular pH and affect the CVR (7,60,62,97,109). Although hypoxic cerebral vasodilation is thought to be primarily related to an increase in adenosine followed by increased K^+ concentrations, a decrease in extracellular pH seen with hypoxia also causes a delayed vasodilation (7,67,111). Both mild hypercapnia (PCO_2 of 50-60 mmHg) and severe hypoxia

(PO_2 <40 mmHg) increase the cerebral glycolytic rate and produce tissue lactoacidosis (95) which tends to reduce tissue pH and further affect CVR. Thus, superimposed metabolic factors which also may lead to cerebral vasodilitation may enhance the CVR-altering effects of either increased PCO_2 or decreased PO_2.

In clinical situations where brain injury occurs, post-traumatic apnea and reduced ventilation are commonly seen (24,90). Ventilatory insufficiency is also common in experimental head injury (86,87,93,94). If chemical regulation of CBF is impaired owing to brain injury, hypoxemia from ventilatory depression may become a complicating factor affecting recovery of the wounded brain (78,105). When chemical regulation of CBF does not occur a subsequent hypercapnic-hypoxemic insult will not be associated with the normally expected increase in CBF. Failure of CBF to increase with hypercapnic-hypoxia might lead to diminished cerebral oxygenation and impairment in brain energy production. This could lead to additional damage to brain cells. Therefore, knowledge regarding the integrity of chemical regulation of CBF after BMW is extremely important.

In our experiments, before wounding, hypercarbia and hypoxia both increased total CBF and decreased total CVR. After wounding, cerebral blood vessel reactivity to both hypercapnia and hypoxia was globally impaired. Most of the individual brain areas evaluated also failed to show a CBF increase in response to increased arterial PCO_2 or decreased arterial PO_2. After wounding the periwound areas (both gray and white) demonstrated 41% reduction in their blood flow when challenged by an increase in PCO_2. Hypoxic challenge following BMW also produced a 50% decrease in periwound gray matter and 29% reduction in periwound white matter rCBFs, (Figs V-B and VI-B). Owing to the small number of animals in these experiments these periwound rCBF reductions did not achieve statistical significance. These findings are suggestive, however, that injured brain about the wound track acts paradoxically to a hypercarbic or hypoxic challange following BMW. It is unlikely that this periwound rCBF reduction represents a physiological, non-uniform rCBF response to blood gas alterations (91) because this post-wounding rCBF decrease occurred primarily in the damaged tissues surrounding the wound track rather than randomly throughout the brain. The decrease in periwound CBF in response to the hypercarbic or hypoxic challenge could be explained either on the basis of a "steal" of blood from non reactive vasculature about the wound track to more normally reactive brain blood vessels or by an actual <u>increase</u> in CVR about the wound in the response to hypoxia or hypercarbia. This latter would represent a <u>very</u> abnormal response.

<u>Possible effect on increased ICP (reduced CPP) on chemical regulation of CBF</u>

Impaired vascular reactivity to either hypoxia, hypercapnia or the combination of both have been also demonstrated in cats subjected to fluid-percussion injury and other experimentally induced cerebral trauma (2,77,114,137,138). Lewelt et al (77), studied the effects of hypoxia and hypercapnia on cerebrovascular reactivity in two separate groups of cats sustaining either mild or severe fluid percussion injury. Severely traumatized cats had a greatly attenuated CBF increase to hypoxemia (PO_2s of 53 and 30 mmHg) or hypercapnia of 54 mmHg. In these experiments the ICPs

increased from a control of 12 mmHg to 44 mmHg immediately after severe injury. The increased ICPs declined rapidly, however, and were at control levels during post-percussion hypoxic and hypercapnic trials when cerebral vascular reactivity to hypercarbia and hypoxia were seen to be imparied. In Lewelt's mildly concussed cats the ICPs were not substantially increased, at any time after injury. Nevertheless, these cats, too, demonstrated impaired CVR responses to increased PCO_2 or decreased pO_2. It, thus, appears unlikely that these impaired chemical responses noted by Lewelt were caused by ICP increases alone. The level of ICPs and CPPs observed in our studies related to chemical regulation after BMW were: ICP 39 to 60 mmHg and CPP 71 to 78 mmHg. Cecil et al (14) have demonstrated, in hypoxic lambs at least, that increases in ICP to about 60 mmHg did not affect cerebral vasodilation in response to severe hypoxia of around 30 mmHg. Data from the afore mentioned experiments are suggestive that an ICP increase alone was not sufficent to abolish chemical CBF regulation in our brain-wounded cats. The effect of ICP alone on both mechanical and chemical CBF regulation will be investigated further in our model.

Possible biochemical factors affecting chemical regulation of CBF

While our experiments have clearly elucidated the effects of missile wounding upon mechanical and chemical regulation of CBF, we have not examined the biochemical perturbations caused by missile wounding. A vast literature exists on substances which regulate cerebral resistance vessels. In all likihood CVR is altered not by a single factor but by interactions of various local chemical regulators such as: H^+, K^+, Ca^{++}, adenosine, brain tissue PO_2 plus other mediators including neurotransmitters (4,6,8,9,12,38,50,57,61,63,66,115,127,137,139). How these substances are affected by brain wounding is totally unknown but clearly deserves future study.

Possible brain stem effects altering chemical regulation of CBF

Crockard et al (18,19,20) and Gerber (37) studied the effects of BMW in primates and demonstrated that brain stem effects were common even though the missile trajectory was several centimeters from the brain stem. Brain stem dysfunction was manifest by cardiovascular changes seen immediately upon wounding. Our studies on brain wounding confirm this effect (13) and we hypothesize significant transfer of missile enrgy to the brain stem. Shalit et al (116) showed that cryogenic lesions of the mid-brain, pons, or upper medulla in dogs abolished the ability of canine cerebral blood vessels to react normally to CO_2. Lesions made in the high spinal cord, lower medulla, cerebellum, thalamus, and cerebral hemispheres did not abolish this response. Shalit's study points to the possible existence of brain stem vasoregulatory centers for CO_2 reactivity within the brain. In our experiments such centers could have been impaired consequent to energy transfer from missile to the brain stem thus abolishing CBF regulation. Saunders et al (114) observed a significant impairment of CO_2 reactivity following fluid-percussion injury to the brain and felt that trauma to the brain stem vasoregulatory centers may have accounted for this.

Our data suggest that following BMW normal chemical regulatory mechanisms for CBF control may be entirely lost throughout the brain. No

compensatory increase in CBF to maintain normal brain metabolism will occur if hypoxia supervenes.

EFFECT OF BMW AND HEMORRHAGE ON ORGAN BLOOD FLOW (OBF)

Brain injury or wounding affects not only the brain but the organism as a whole. Cardiovascular and respiratory abnormalities have long been noted following brain injury (16,19-21,37,53,75,87,136) Studies on the effect of BMW on OBFs are almost not existant and include only the evaluation of cardiac output, renal and femoral blood flows in the primate (75).

The question arises whether BMW, with or without concomitant systemic hemorrhage, could also affect blood flow in vital organs as lung, heart and kidney? If so, post wounding ischemia in these organs would become an additional insult after BMW and add to the burden of the brain wound. Ischemia in various organs might then impair recovery of the brain-wounded individual. We, thus, thought it important to measure OBF to determine the interaction of BMW with at least this one aspect of peripheral organ function.

Our data suggest that multiple organs sustain decreases in blood flow following a brain wound even though the animal remains normotensive. If the animal sustains a BMW and hemorrhagic hypotension simultaneously blood flow in the kidney, adrenals, and spleen show significant decreases. While decreased OBF might be expected with simultaneously occurring BMW plus HH the tendency to reduced OBF following a BMW alone in normotensive cats is interesting and suggests that BMW IN THE CAT INDUCES, IN MOST PERIPHERAL ORGANS, A STATE CONSISTANT WITH HEMORRHAGIC SHOCK DESPITE A NORMAL MABP.

Hemorrhagic hypotension in our unwounded cats produced OBFs similar to those observed in various species (21,33,72,120). Slater et al (120), measured OBFs during hemorrhagic shock and after reinfusion in unanesthetized dogs. They reduced MABP to 50 mmHg over 3-4 hours and then reinfused the shed blood. The early response to hemorrhage consisted of a redistribution of cardiac output favoring the heart and brain. Blood flows to brain, heart were reduced, however, as was adrenal flow. The kidney and, in particular spleen, showed extreme reductions in their flows. Immediately after the return of the shed blood, OBFs again approximated control levels. In our hypotensive unwounded cats too, reinfusion reestablished blood flow in most organs (Fig 10). Laughlin (72), measured OBF (microspheres) during HH in anesthetized miniature swine at MABPs of 65,50,35 and 20 mmHg for 10-15 min at each stage. He found that HH consistantly decreased myocardial and renal blood flows as well as flows to most other organs. Blood flow to the brain however, did not change significantly at any level of hypotension. Except for the decreased heart blood flow Laughlin's experiments are in agreement with our data for unwounded hypotensives cats.

The pattern of OBF reduction in our brain-wounded, hypotensive cats was similar to that observed in hypotensive unwounded cats (Figs 10 and 11). Interestingly, cardiac blood flow showed no significant change indicating that, taken together, the effects of BMW and HH on cardiac blood flow cancelled each other. Reinfusion, of shed blood restored OBF in these cats but, as we have shown, CBF was not reestablished.

MICROSPHERE SHUNTING

Microsphere shunting in a normotensive unwounded cat, a normotensive wounded cat and an unwounded hypotensive cat were all less than 1%. The calculated CBFs in these animals were, therefore, probably quite representative of true flows. Several attempts were made to obtain sphere samples from the sagittal sinus of wounded hemorrhagic cats. CBFs became reduced and sampling spheres from the sagittal sinus became impossible. Further attempts at obtaining sagittal sinus spheres in BMW-HH cats will be made to ascertain that C = 0. Likewise, sagittal sinus sphere samples will be obtained in hypercapnic and hypoxic cats to make sure significant shunting does not occur under these conditions. Inferior vena cava blood samples will also be obtained to make sure that OBFs are realistic. We will not sample the venous outflow from individual organs but rely on inferior vena cava samples to estimate the degree of shunting for non-brain organs as a whole.

MILITARY MEDICAL SIGNIFICANCE

If our experiments on the brain-wounded cat may be extrapolated to humans they suggest the following:

1) THE UNWOUNDED BRAIN CAN MAINTAIN ADEQUATE CBF THROUGH AUTOREGULATORY MECHANISMS:

a) WHEN THERE IS A SUBSTANTIAL BLOOD LOSS
b) WHEN, THROUGH HEMORRHAGE, MABP FALLS TO ~40 mmHg AT LEAST UP TO 45 MINUTES AFTER THE ONSET OF WOUNDING;
c) WHEN CONCOMITANT, MILD METABOLIC ACIDOSIS EXISTS.

2) THE MISSILE-WOUNDED BRAIN CANNOT MAINTAIN MECHANICAL REGULATION OF CBF AND IS IN GREAT JEOPARDY IF A BRAIN WOUND IS ACCOMPANIED BY SIGNIFICANT BLOOD LOSS WHICH REDUCES MABP EVEN SLIGHTLY. THIS SEQUENCE OF EVENTS MAY LEAD TO FATAL, IRREVERSIBLE CEREBRAL ISCHEMIA. IT IS, THUS, ABSOLUTELY IMPERATIVE THAT MABP BE MAINTAINED IN A PERSON WHO HAS SUSTAINED A BRAIN WOUND.

3) ONCE ISCHEMIC, THE MISSILE-WOUNDED BRAIN MAY NOT BE ABLE TO BE REPERFUSED. REPERFUSION FAILURE HAS STARK IMPLICATIONS FOR COMBAT MEDICAL CARE: IF A BRAIN-WOUNDED SOLDIER ALSO SUFFERS CONCOMITANT, SUBSTANTIAL BLOOD LOSS AND IF CBF FALLS SIGNIFICANTLY BELOW NORMAL, IT MAY BE IMPOSSIBLE TO IMPROVE CBF AND SALVAGE THE BRAIN DESPITE ADEQUATE BLOOD REPLACEMENT AND MABP RESTORATION. THIS FACT REINFORCES THE PRIOR CONCLUSION THAT IT IS IMPERATIVE TO MAINTAIN MABP AND CBF IN A BRAIN-WOUNDED SOLDIER.

4) WHILE IT IS IMPORTANT TO MAINTAIN ADEQUATE ARTERIAL OXYGENATION IN ALL WOUNDED PATIENTS, IT IS CRITICAL TO DO SO IN THOSE WITH A BRAIN WOUND BECAUSE THE MISSILE-WOUNDED BRAIN LOSES ITS ABILITY TO CHEMICALLY REGULATE CBF AND COMPENSATE FOR SUPERIMPOSED HYPOXIA.

5) A MISSILE WOUND TO THE BRAIN MAY SERIOUSLY IMPAIR CIRCULATION IN PERIPHERAL ORGANS QUITE DISTINCT FROM ITS EFFECT ON CBF. RECOVERY OF A BRAIN-WOUNDED SOLDIER MAYBE IMPAIRED BY PERIPHERAL ORGAN CIRCULATORY DYSFUNCTION AS WELL AS BY THE BRAIN WOUND ITSELF

RECOMMENDATIONS

THAT POST WOUNDING BRAIN REPFERSUION FAILURE BE THOROUGHLY INVESTIGATED TO DETERMINE:

1) AT WHAT CRITICAL MABP LEVELS AND TIMES POST WOUNDING ISCHEMIA OCCURS

2) MECHANISMS UNDERLYING BRAIN REPERFUSION FAILURE

3) POSSIBLE TREATMENTS OF THIS CONDITION

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Section B

Plasma Catecholamines After Brain Wounding and Increased Intracranial Pressure

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INTRODUCTION

During the April 1987--April 1988 interval we acquired and installed our high pressure liquid chromatograph (HPLC) system (Aug.'87) and developed an assay system to measure plasma catecholamines (CAs) in cats. The assay system was quite complex and required much initial development and validating.

From Dec.'87 through May '88 we have analyzed the effects of missile wounds to the brain on the plasma CAs: norepinephrine (NE) and epinephrine (EPI). The plasma CAs are of interest because high circulating levels of plasma CAs may have deleterious effects on the cardiovascular and pulmonary systems, basal metabolic rate and neuronal function in the CNS (1). Circulating CAs do not normally cross the blood-brain barrier (BBB) and enter the brain. However, missile wounds to the brain do break down the BBB and plasma CAs do enter the brain. Such abnormal entry could affect local microcirculation and directly affect brain neuronal function (4). Therefore, delineating the effect of missile wounds to the brain on plasma CAs may be of importance because this systemic effect of brain wounding may, in turn, affect brain function particularly in the area where the BBB is damaged.

Increases in intracranial pressure (ICP) alone, without injury, has been shown to increase the levels of plasma CAs (2). Since missile wounds to the brain caused dramatic elevations in ICP, adjunct experiments were performed to determine the contributions, if any, of increased intracranial pressure (ICP) on the plasma CAs and the time course of the CA response. It was anticipated that the time course of plasma CA responding may be different in brain-wounded animals with elevated ICP than in non-brain-wounded animals with elevated ICP.

Additionally, in order to determine if the physiological and biochemical responses may be a function of trajectory angle, our standard anterior to posterior (AP) trajectory was changed to a transverse trajectory . It was hoped that the results would aid in determining whether the plasma CA responding was a function of brain area(s) injured and/or level of ICP induced due to injury.

PART 1. BRAIN INJURY EXPERIMENTS

Using our standard AP trajectory through the right hemisphere, animals were injured at 0.9J, 1.4J and 2.4J. Unwounded controls were also included. Variables quantified include: mean arterial blood pressure (MABP), ICP, cerebral perfusion pressure (CPP), plasma NE, plasma EPI and plasma glucose. Blood samples were drawn at 1,3,5,10,20,30 and 60 minutes after the start of the experimental period (controls) or post-injury (experimental groups). All the data (raw, means, and sem) are presented in tables 1-6 and are also graphically presented for ease of viewing (figs.1-10).

When statistical analyses were performed the data were first analyzed by ANOVA, then individual comparisons were made using Dunnett's test. Asterisks (*) = $p < .05$ or more when compared to TIME "0" (control period). Asterisks appear on graphed data ONLY.

A. Controls (fig.1A-F, tables 1-6)--Controls received the same treatment and surgical preparations as the injured groups except no injury was induced. There were no effects on any variable caused by surgical preparation or procedures.

B. 0.9J Injury (fig.2A-F, tables 1-6)--This injury caused no significant changes on MABP, ICP or CPP during any time period. Plasma NE and EPI, however, were significantly elevated at 1 min.(only) and plasma glucose displayed a significant rise at 5 min. and remained so for the duration (60 min.).

C. 1.4J Injury (fig.3A-F, tables 1-6)--This injury level caused significant elevations in MABP, ICP, and depressed CPP at 1 and 3 mins. The ICP remained significantly elevated for 10 mins. and the CPP remained depressed for the duration. Plasma NE and EPI were DRAMATICALLY elevated at 1 and 3 mins., while plasma glucose was elevated at 5 mins and remained elevated for the duration.

D. 2.4J Injury (fig.4A-F, tables 1-6)--This injury level caused significant elevations in MABP, ICP and depressed CPP at 1 min. The ICP remained significantly elevated for 10 mins. and the CPP depressed for the duration. Plasma NE and EPI were DRAMATICALLY elevated at 1 and 3 mins., but returned to near baseline levels by 5 to 10 mins. Plasma glucose was significantly elevated at 5 mins. and remained so for the duration.

E. Since figs. 1-4 present all the physiological and biochemical data for individual experimental groups, the data are re-presented in figs. 5-10 such that the results of ALL experimental groups for each physiological and biochemical variable are presented on one graph. This type of presentation allows for easy comparison of results across all the experimental groups.

Discussion

The data suggest that there are differences in responding between the 0.9J and 1.4J or 2.4J energy shots, but 1.4J and 2.4J shots are very similar in the parameters measured. For instance, all injury levels caused immediate (1 min) rises in ICP and MABP, but the rises were significant only for the 1.4J and 2.4J groups. Likewise, the CPPs were significantly depressed from 1 to 60 mins. only in the 1.4J and 2.4J groups. However, at ALL injury levels there were significant and immediate (1 min) elevations in plasma NE and EPI, but the magnitude of the responses was quite different between the 0.9J and the 1.4J or 2.4J groups. In all elevations, the CA rose quickly then diminished to non-significant or baseline levels within 5 to 10 mins. The glucose levels showed an expectedly slower response in all groups, not becoming elevated until 5 mins. and remaining there for the duration. The magnitude of the glucose response was related, as expected, to the magnitude of ths plasma EPI response.

The significance of these results is that ALL injury levels resulted in immediate and significant elevations in plasma CAs, which appear to be related to the increase in MABP, whether significant or not, in response to an increase in ICP.

Fig 1 (A-F). PHYSIOLOGICAL AND BIOCHEMICAL RESULTS IN CONTROL (UNWOUNDED) CATS

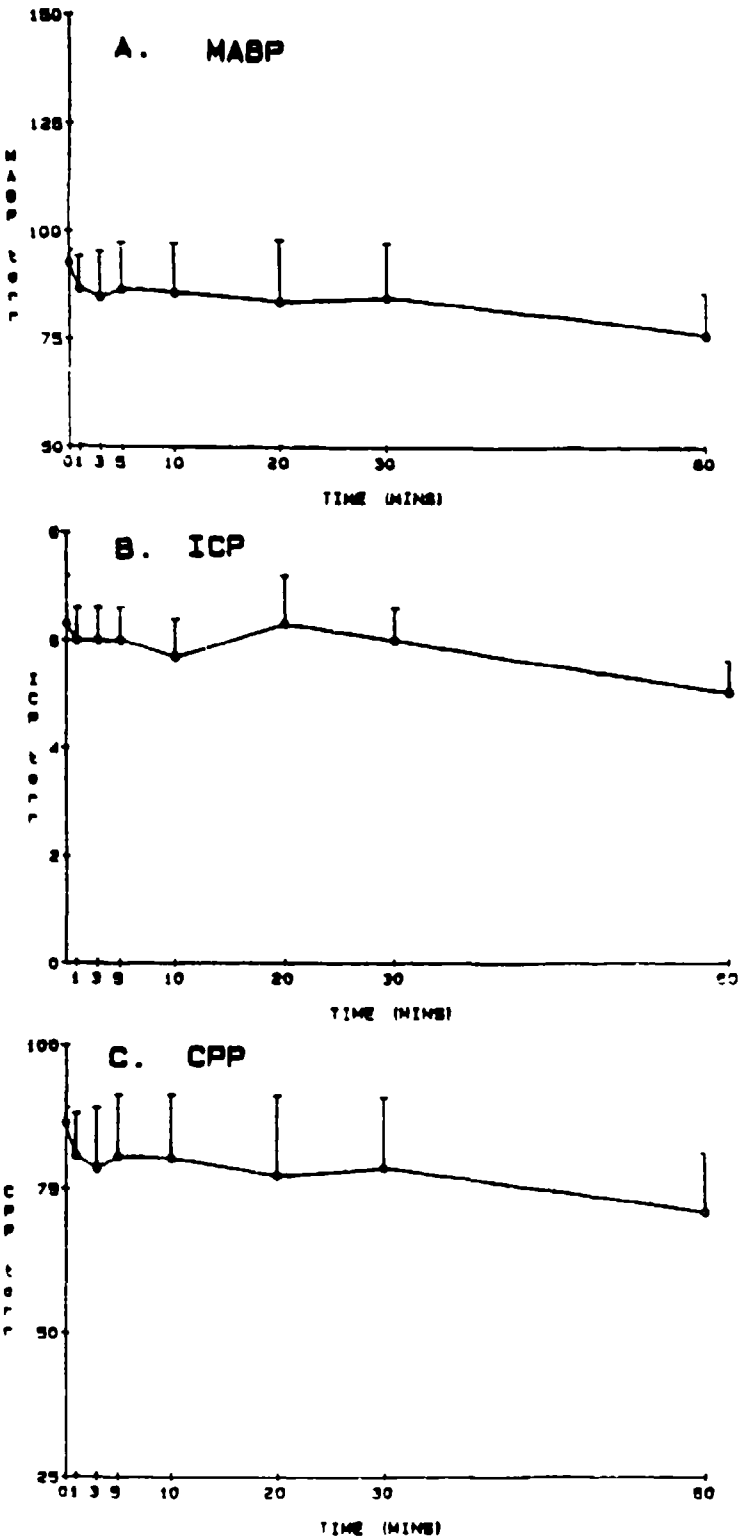


Fig 1. (cont'd)

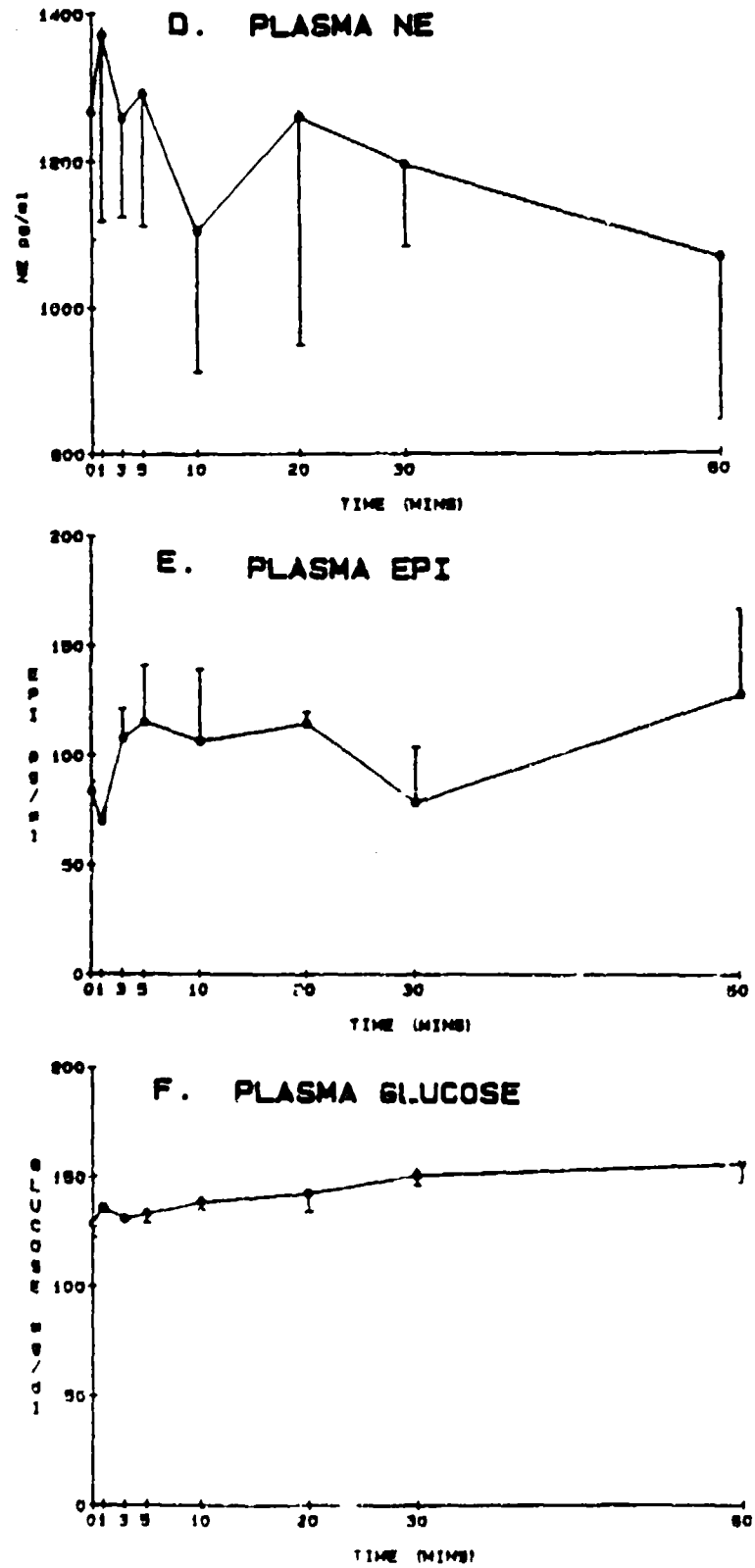

D. PLASMA NE
1400
1200
1000
800
NE pg/ml
0 1 3 5 10 20 30 60
TIME (MINS)
E. PLASMA EPI
200
150
100
50
0
EPI pg/ml
0 1 3 5 10 20 30 60
TIME (MINS)
F. PLASMA GLUCOSE
200
150
100
50
0
mg/dl
0 1 3 5 10 20 30 60
TIME (MINS)

Fig 2 (A-F). PHYSIOLOGICAL AND BIOCHEMICAL RESULTS IN 0.9J WOUNDED CATS

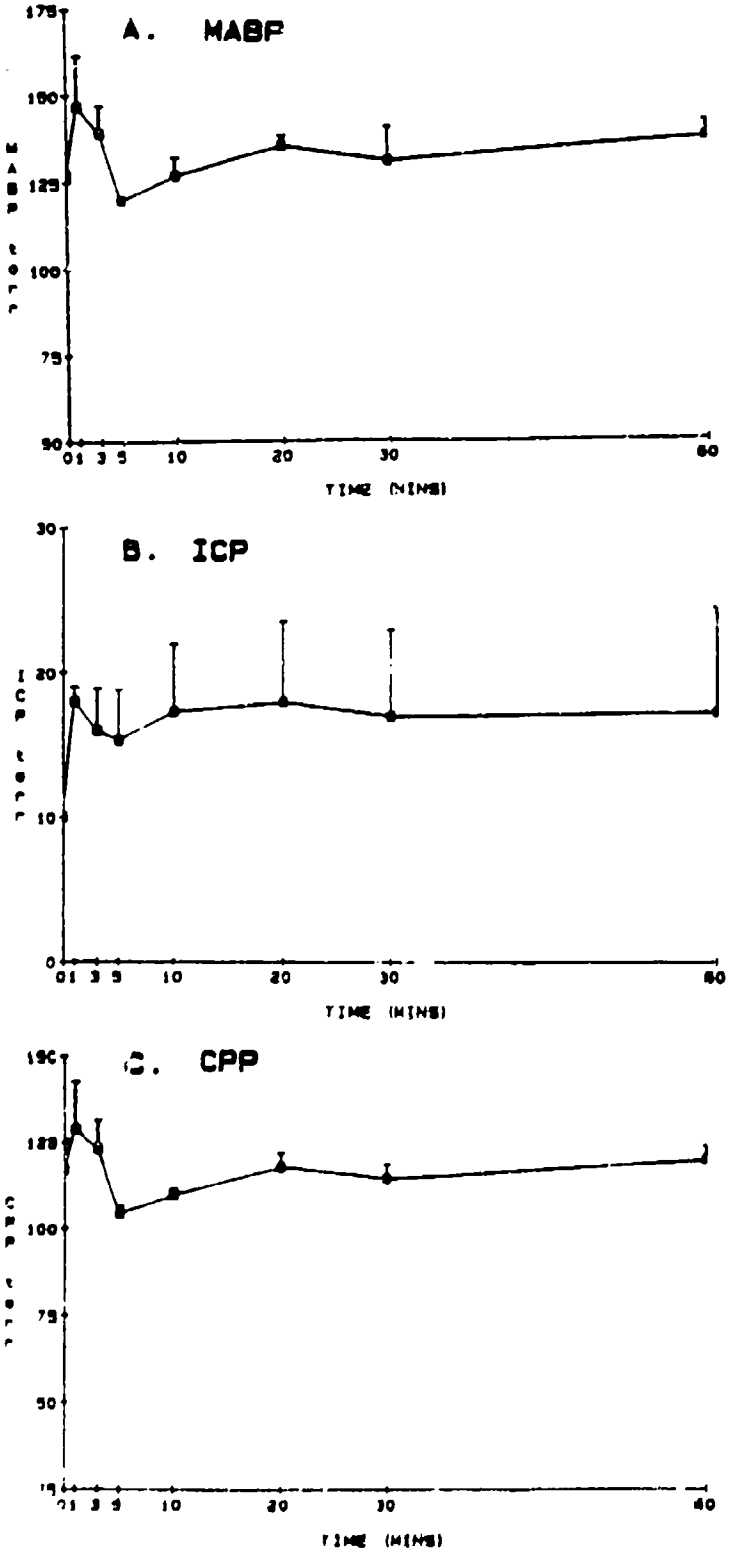


Fig 2. (cont'd)

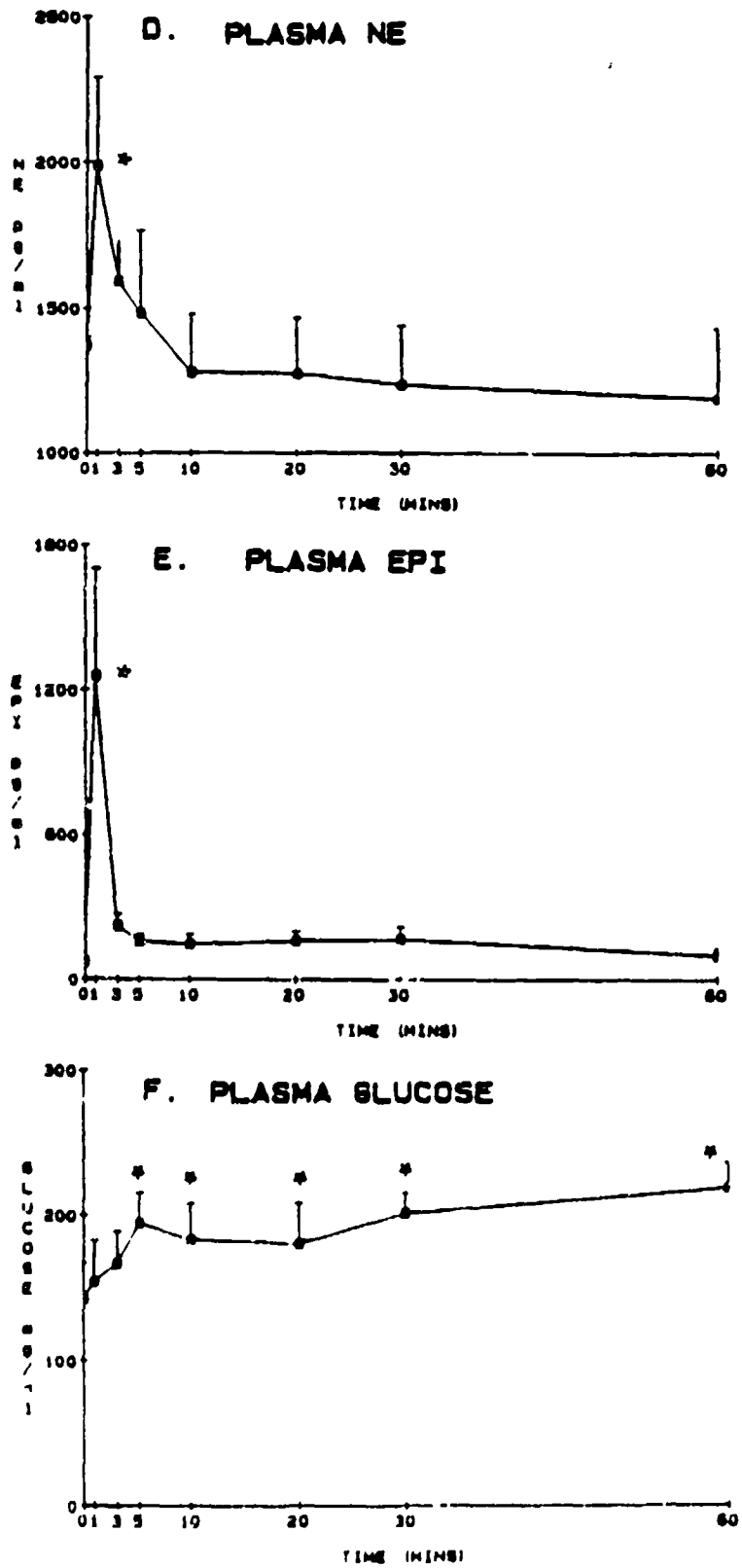
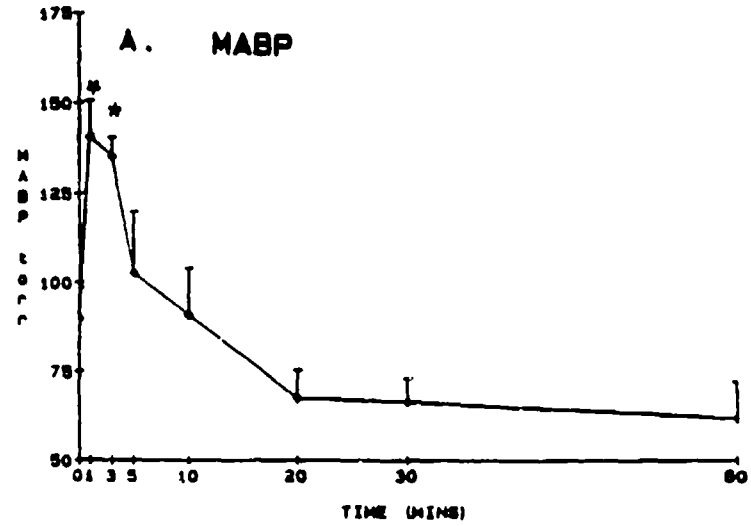
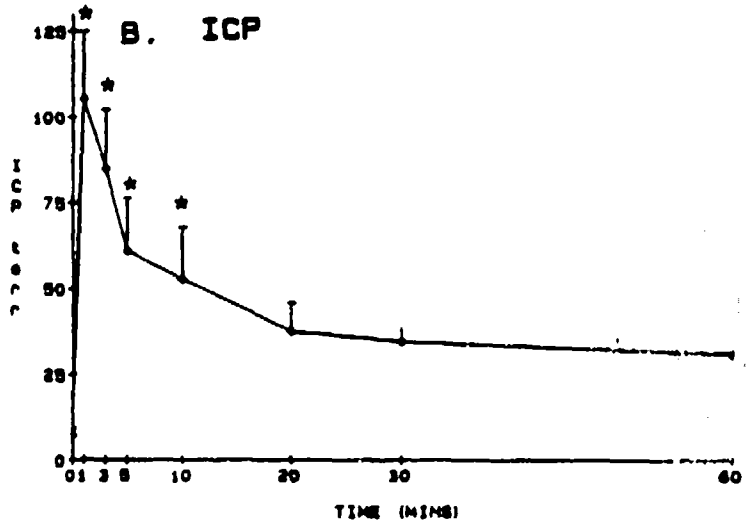

D. PLASMA NE
NE pg/ml
2500
2000
1500
1000
01 3 5 10 20 30 60
TIME (MINS)
E. PLASMA EPI
EPI pg/ml
1800
1200
600
0
01 3 5 10 20 30 60
TIME (MINS)
F. PLASMA GLUCOSE
GLUCOSE mg/dl
300
200
100
0
01 3 5 10 20 30 60
TIME (MINS)

Fig 3 (A-F). PHYSIOLOGICAL AND BIOCHEMICAL RESULTS IN 1.4J WOUNDED CATS





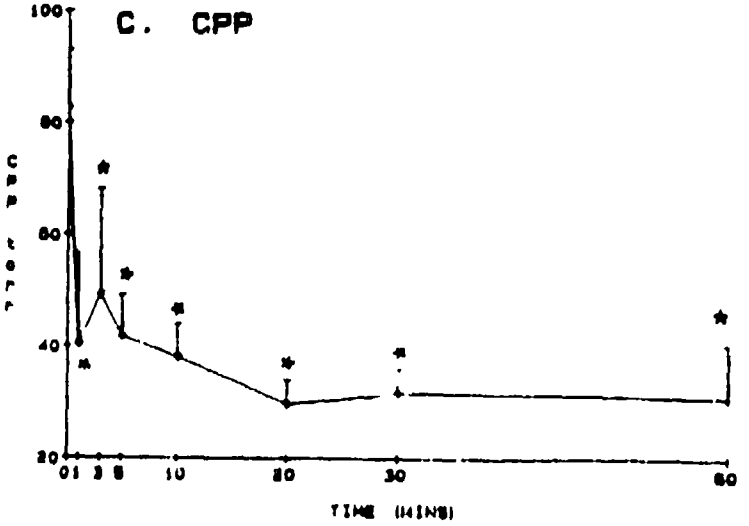


Fig 3. (cont'd)

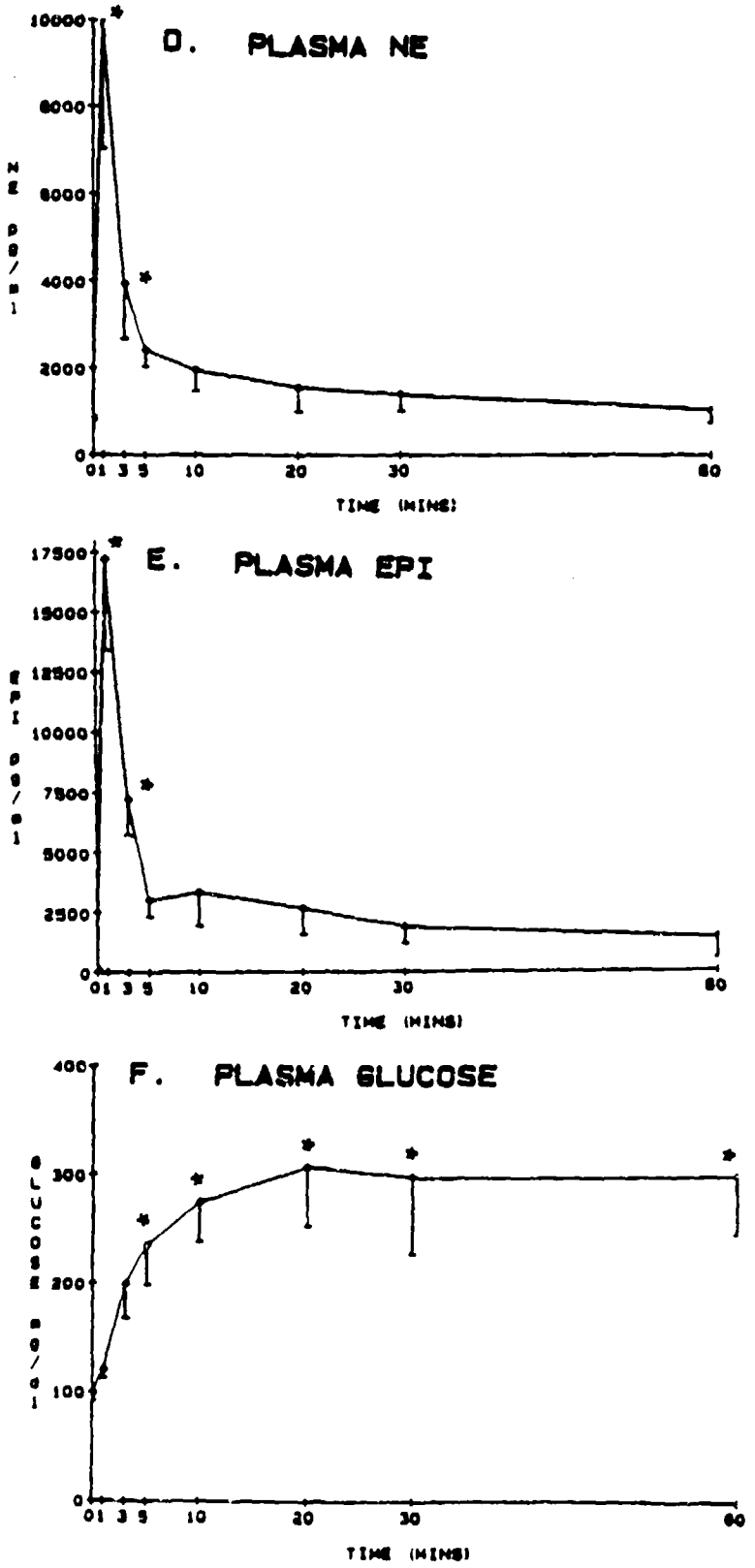

D. PLASMA NE
NE pg/ml
10000
8000
6000
4000
2000
0
01 3 5 10 20 30 60
TIME (MINS)
E. PLASMA EPI
EPI pg/ml
17500
15000
12500
10000
7500
5000
2500
0
01 3 5 10 20 30 60
TIME (MINS)
F. PLASMA GLUCOSE
GLUCOSE mg/dl
400
300
200
100
0
01 3 5 10 20 30 60
TIME (MINS)

Fig 4 (A-F). PHYSIOLOGICAL AND BIOCHEMICAL RESULTS IN 2.4J WOUNDED CATS

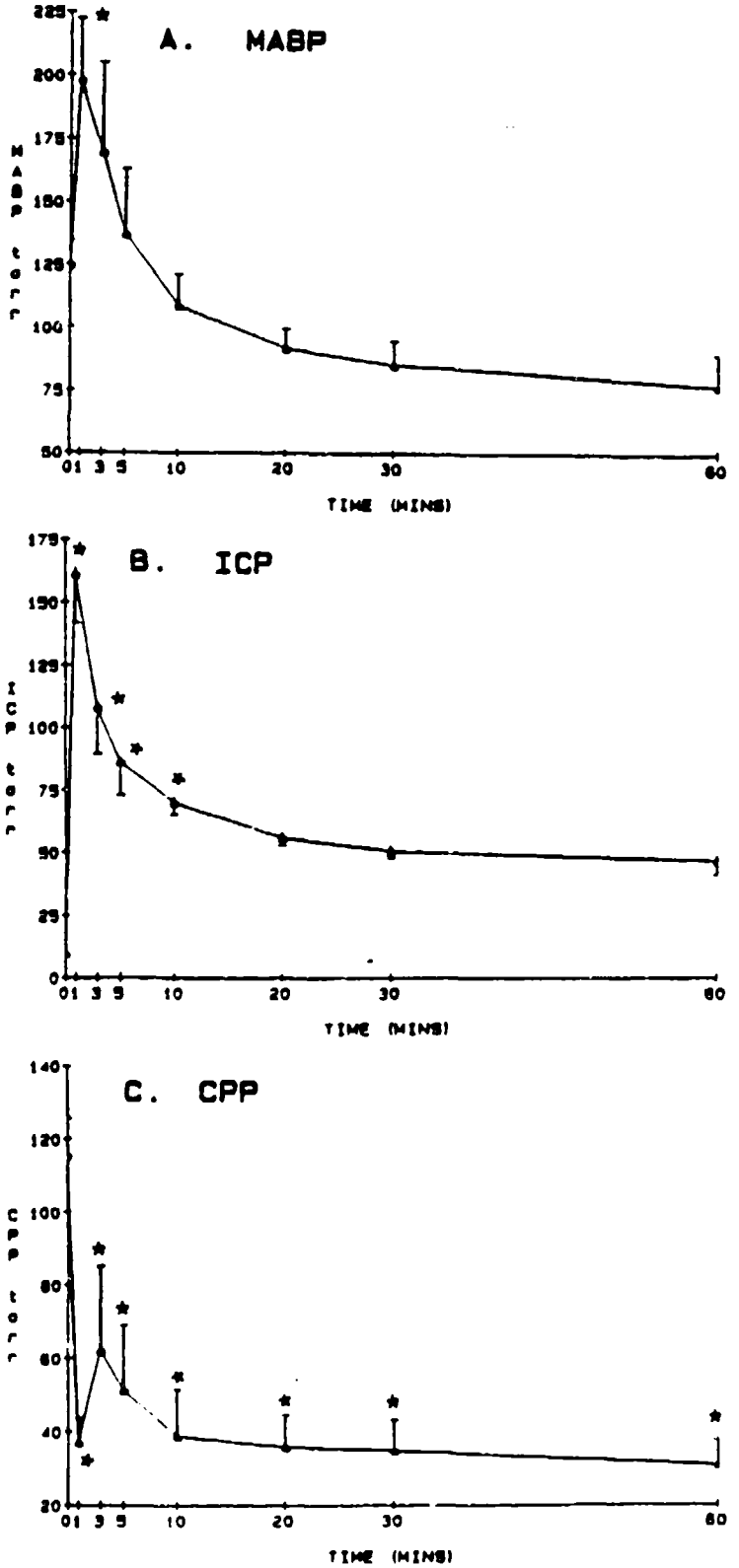


Fig 4. (cont'd)

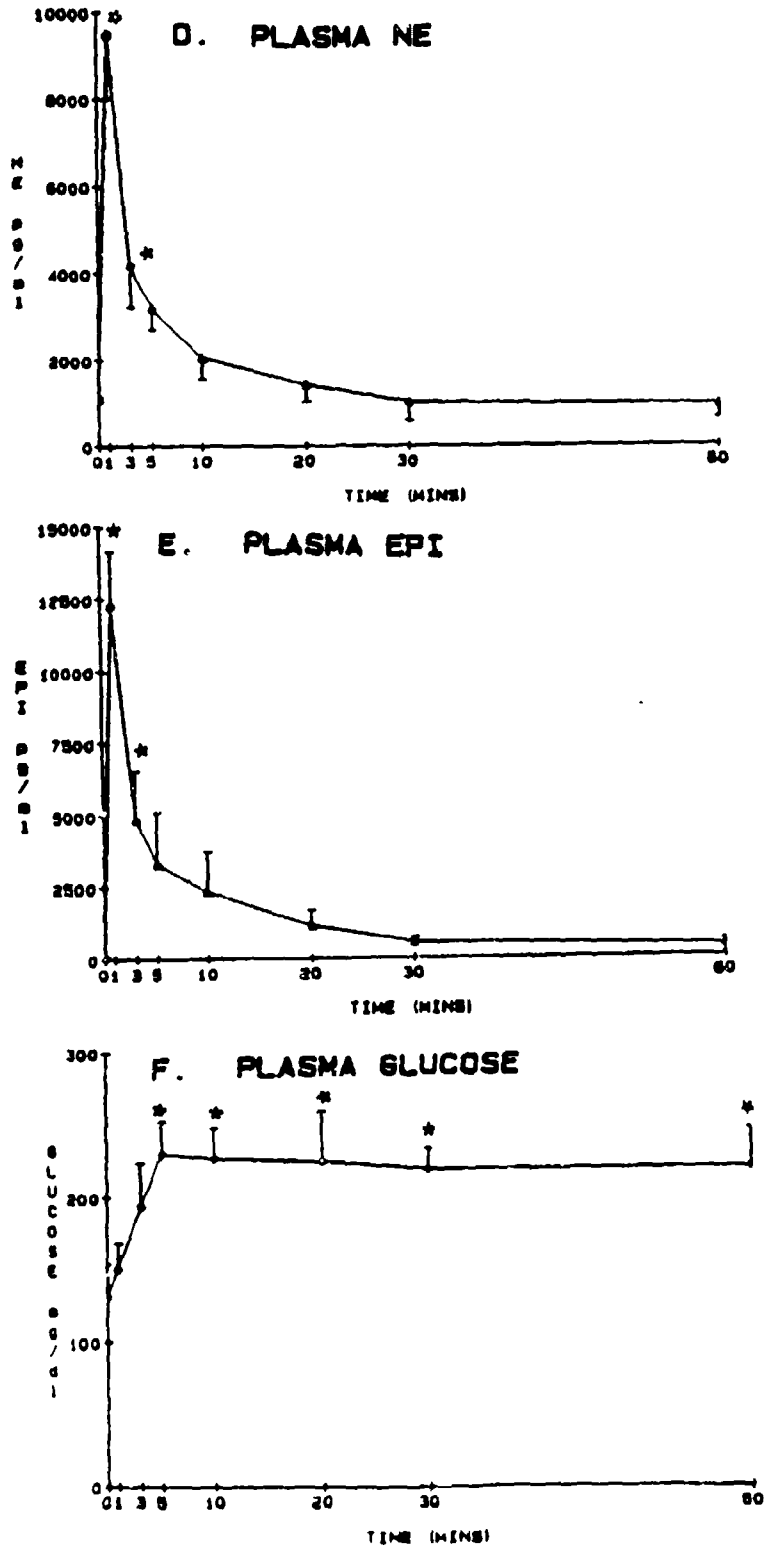
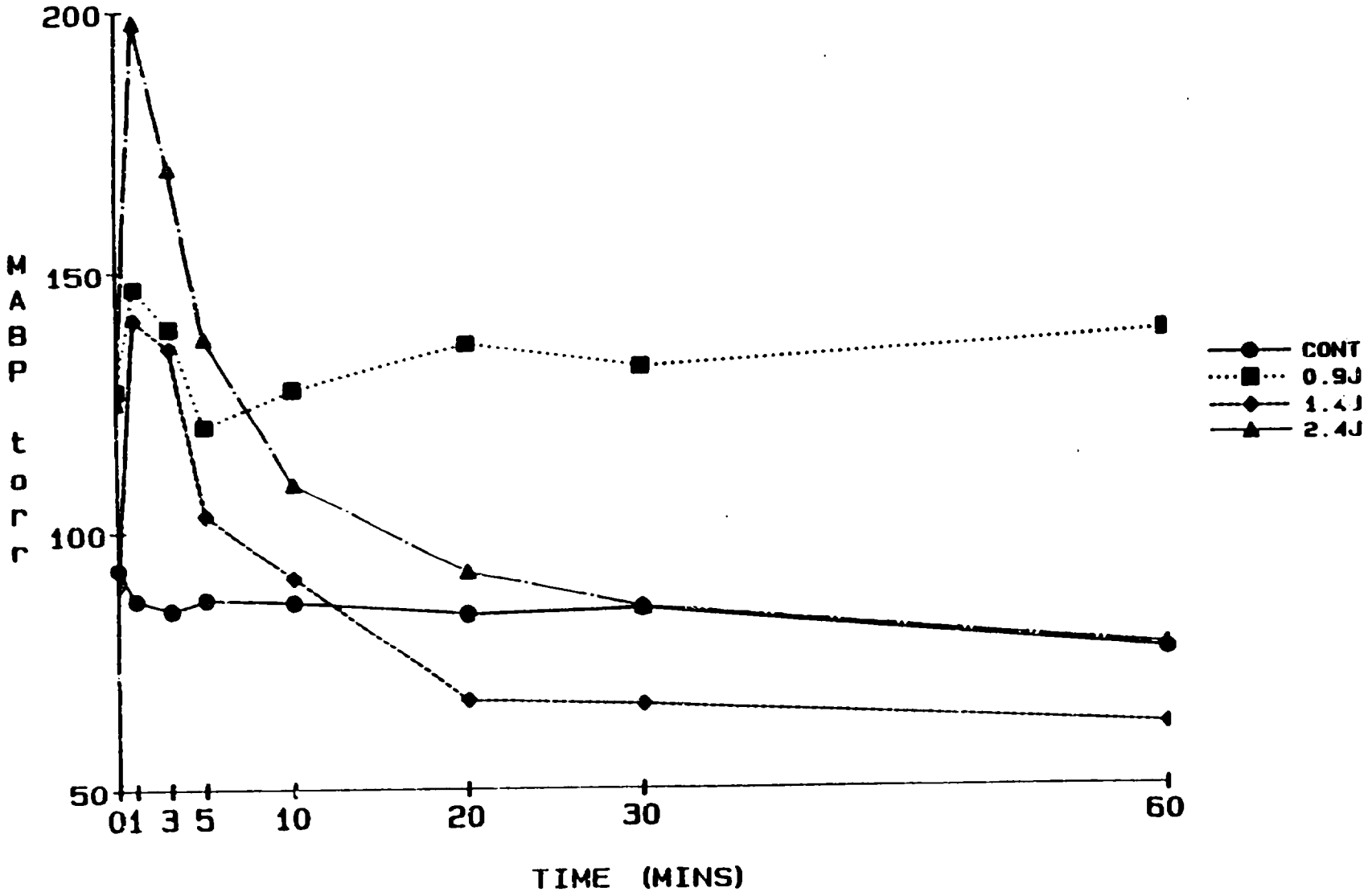

D. PLASMA NE
NE pg/ml
10000
8000
6000
4000
2000
0
01 3 5 10 20 30 60
TIME (MINS)
E. PLASMA EPI
EPI pg/ml
15000
12500
10000
7500
5000
2500
0
01 3 5 10 20 30 60
TIME (MINS)
F. PLASMA GLUCOSE
GLUCOSE mg/dl
300
200
100
0
01 3 5 10 20 30 60
TIME (MINS)

Fig 5. MEAN ARTERIAL BLOOD PRESSURE IN WOUNDED CATS



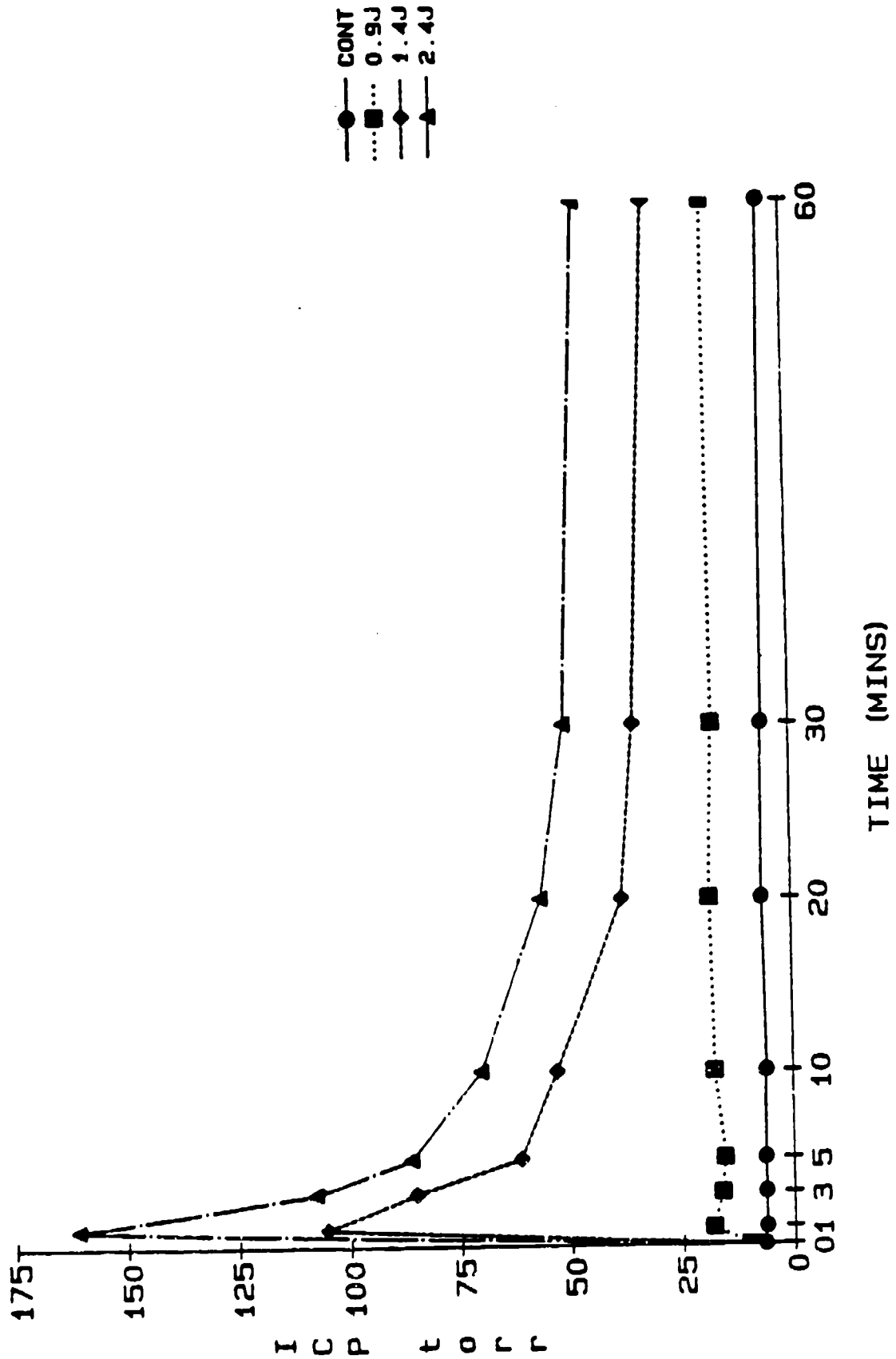


Fig 6. INTRACRANIAL PRESSURE IN WOUNDED CATS

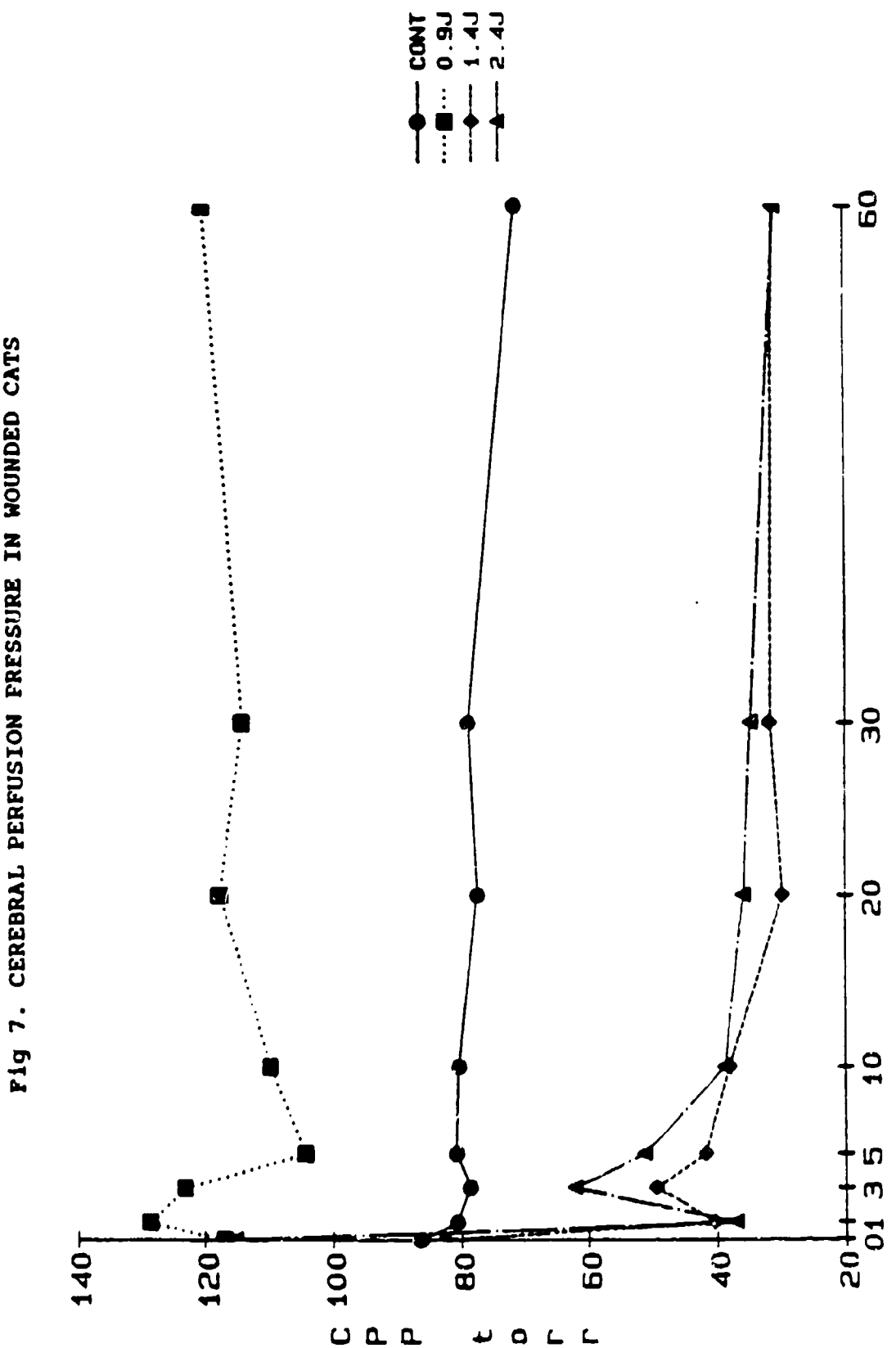


Fig 7. CEREBRAL PERFUSION PRESSURE IN WOUNDED CATS

Fig 8. PLASMA NOREPINEPHRINE IN WOUNDED CATS

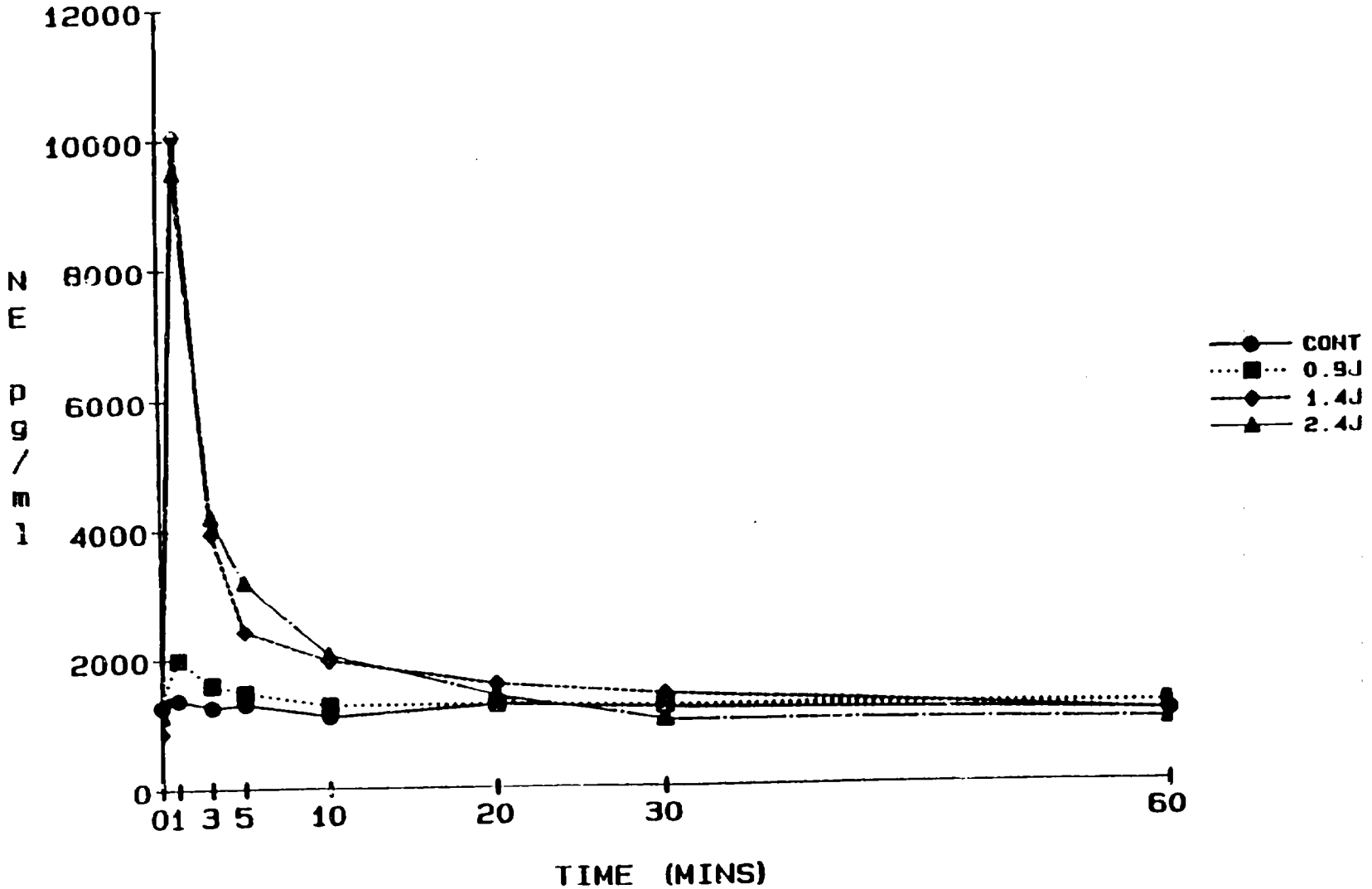


Fig 9. PLASMA EPINEPHRINE IN WOUNDED CATS

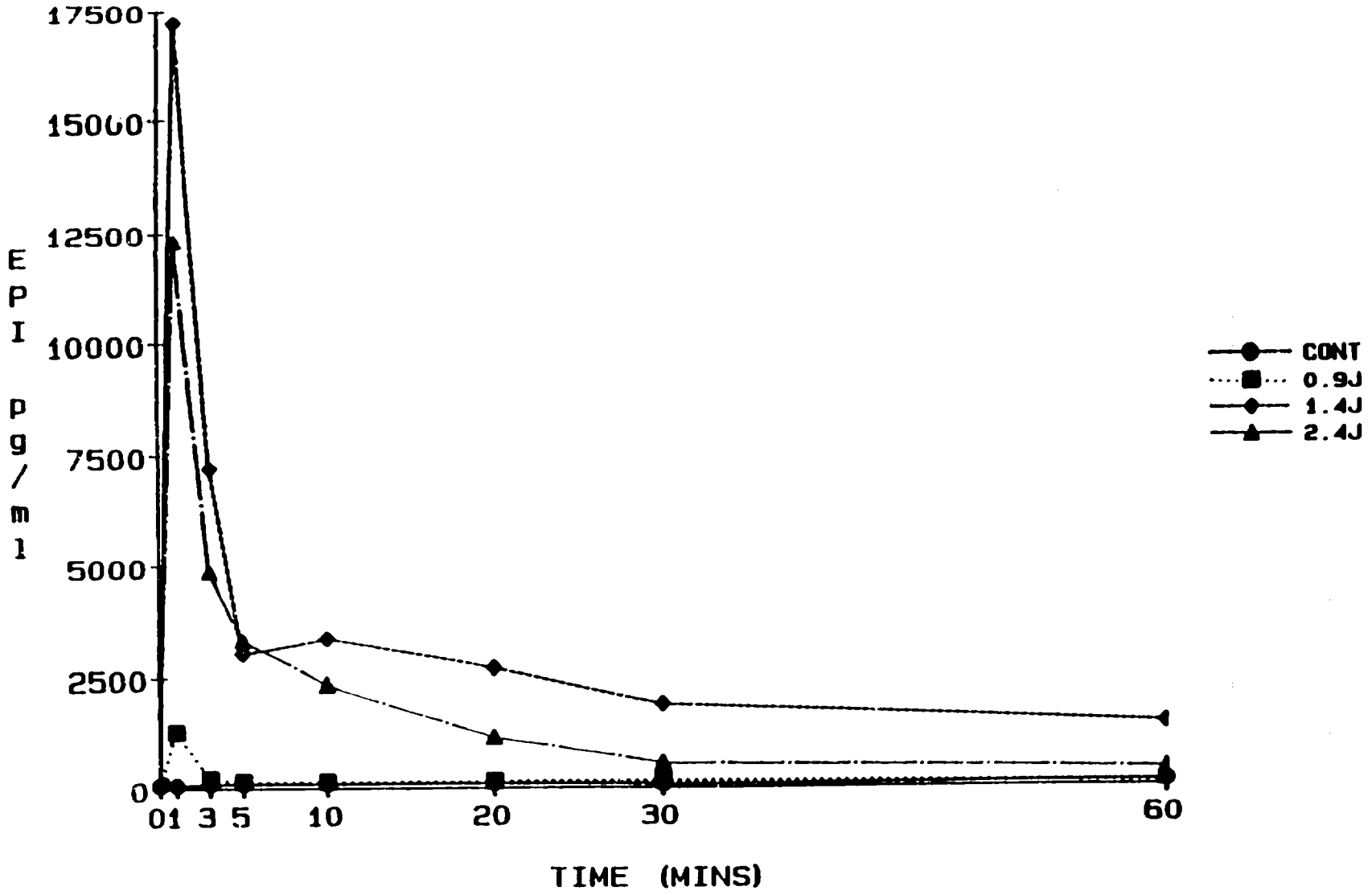


Fig 10. PLASMA GLUCOSE IN WOUNDED CATS

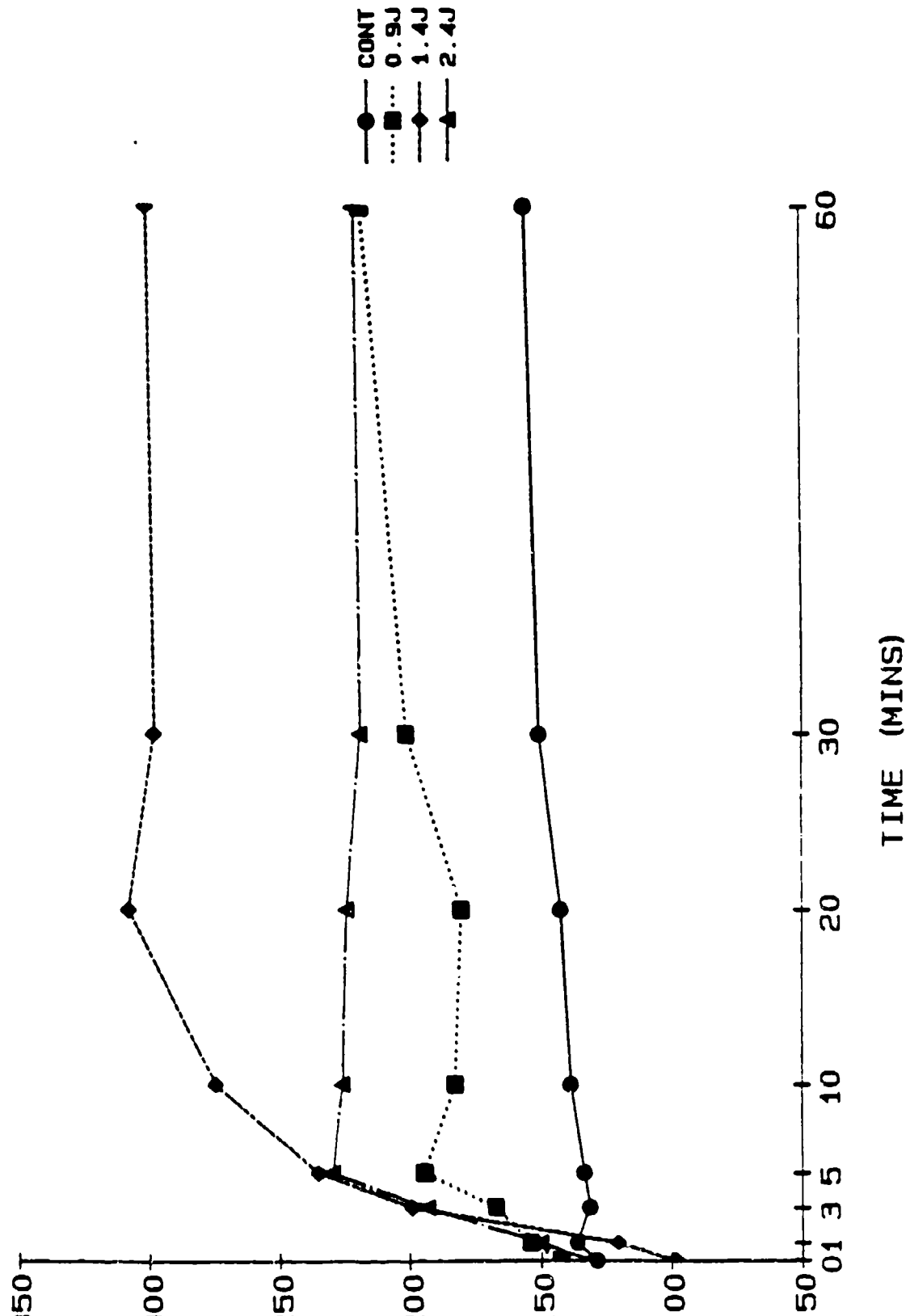


Table 1. MEAN ARTERIAL BLOOD PRESSURE (torr) IN WOUNDED CATS

	CONT	1 MIN	3 MIN	5 MIN	10 MIN	20 MIN	30 MIN	60 MIN
CONTROLS								
CG12	96.0	91.0	91.0	91.0	91.0	91.0	89.0	72.0
CG13	95.0	97.0	99.0	103.0	103.0	104.0	104.0	95.0
CG15	87.0	72.0	64.0	66.0	64.0	56.0	61.0	61.0
MEAN	92.7	86.7	84.7	86.7	86.0	83.7	84.7	76.0
(+/-SEM)	2.8	7.5	10.6	10.9	11.5	14.3	12.6	10.0
0.9 JOULES								
CG7	125.0	147.0	147.0	117.0	117.0	131.0	112.0	131.0
CG9	143.0	121.0	123.0	121.0	129.0	141.0	146.0	146.0
CG11	113.0	172.0	147.0	121.0	135.0	135.0	135.0	136.0
MEAN	127.0	146.7	139.0	119.7	127.0	135.7	131.0	137.7
(+/-SEM)	8.7	14.7	8.0	1.3	5.3	2.9	10.0	4.4
1.4 JOULES								
CG1	97.0	160.0	146.0	126.0	113.0	72.0	79.0	73.0
CG14	72.0	135.0	128.0	113.0	92.0	78.0	64.0	41.0
CG17	100.0	127.0	131.0	69.0	67.0	52.0	56.0	71.0
MEAN	89.7	140.7	135.0	102.7	90.7	67.3	66.3	61.7
(+/-SEM)	8.9	9.9	5.6	17.2	13.3	7.9	6.7	10.3
2.4 JOULES								
CG6	135.0	204.0	177.0	143.0	113.0	107.0	104.0	102.0
CG8	105.0	237.0	227.0	179.0	128.0	87.0	75.0	61.0
CG16	134.0	153.0	105.0	89.0	85.0	81.0	76.0	68.0
MEAN	124.7	198.0	169.7	137.0	108.7	91.7	85.0	77.0
(+/-SEM)	9.8	24.4	35.4	26.2	12.6	7.9	9.5	12.7

Table 2. INTRACRANIAL PRESSURE (torr) IN WOUNDED CATS

	CONT	1 MIN	3 MIN	5 MIN	10 MIN	20 MIN	30 MIN	60 MIN
CONTROLS								
CG12	5.0	5.0	5.0	5.0	5.0	8.0	7.0	6.0
CG13	8.0	7.0	7.0	7.0	7.0	6.0	6.0	4.0
CG15	6.0	6.0	6.0	6.0	5.0	5.0	5.0	5.0
MEAN	6.3	6.0	6.0	6.0	5.7	6.3	6.0	5.0
(+/-SEM)	0.9	0.6	0.6	0.6	0.7	0.9	0.6	0.6
0.9 JOULES								
CG7	10.0	17.0	11.0	9.0	8.0	7.0	5.0	3.0
CG9	10.0	17.0	16.0	46.0	22.0	22.0	24.0	27.0
CG11	10.0	20.0	21.0	21.0	22.0	25.0	22.0	22.0
MEAN	10.0	18.0	16.0	15.3	17.3	18.0	17.0	17.3
(+/-SEM)	0.0	1.0	2.9	3.5	4.7	5.6	6.0	7.3
1.4 JOULES								
CG1	3.0	100.0	90.0	70.0	70.0	50.0	40.0	32.0
CG14	10.0	142.0	112.0	82.0	66.0	41.0	40.0	29.0
CG17	8.0	74.0	53.0	31.0	22.0	22.0	24.0	31.0
MEAN	7.0	105.3	85.0	61.0	52.7	37.7	34.7	30.7
(+/-SEM)	2.1	19.8	17.2	15.4	15.4	8.3	5.3	0.9
2.4 JOULES								
CG6	10.0	158.0	90.0	72.0	61.0	57.0	53.0	57.0
CG8	10.0	196.0	144.0	112.0	77.0	50.0	45.0	40.0
CG16	8.0	129.0	89.0	74.0	72.0	61.0	53.0	42.0
MEAN	9.3	161.0	107.7	86.0	70.0	56.0	50.3	46.3
(+/-SEM)	0.7	19.4	18.2	13.0	4.7	3.2	2.7	5.4

Table 3. CEREBRAL PERFUSION PRESSURE IN WOUNDED CATS

	CONT	1 MIN	3 MIN	5 MIN	10 MIN	20 MIN	30 MIN	60 MIN
CONTROLS								
CG12	91.0	86.0	86.0	86.0	86.0	83.0	82.0	66.0
CG13	87.0	90.0	92.0	96.0	96.0	98.0	98.0	91.0
CG15	81.0	66.0	59.0	60.0	59.0	51.0	56.0	56.0
MEAN	86.3	80.7	78.6	80.7	80.3	77.3	78.7	71.0
(+/-SEM)	2.9	7.4	10.5	10.7	11.1	13.9	12.2	10.4
0.9 JOULES								
CG7	115.0	130.0	136.0	108.0	109.0	124.0	108.0	128.0
CG9	133.0	104.0	107.0	105.0	107.0	119.0	122.0	119.0
CG11	103.0	152.0	126.0	100.0	113.0	110.0	113.0	114.0
MEAN	117.0	128.7	123.0	104.3	109.7	117.7	114.3	120.0
(+/-SEM)	8.7	13.9	8.5	2.3	1.8	4.1	4.1	4.1
1.4 JOULES								
CG1	94.0	60.0	56.0	56.0	43.0	22.0	39.0	41.0
CG14	62.0	8.0	14.0	31.0	26.0	37.0	24.0	12.0
CG17	92.0	53.0	78.0	38.0	45.0	30.0	32.0	40.0
MEAN	82.6	40.3	49.3	41.7	38.0	29.7	31.7	31.0
(+/-SEM)	10.3	16.3	18.8	7.4	6.0	4.3	4.3	9.5
2.4 JOULES								
CG6	125.0	46.0	87.0	71.0	52.0	50.0	51.0	45.0
CG8	95.0	41.0	83.0	67.0	51.0	37.0	30.0	21.0
CG16	126.0	24.0	16.0	15.0	13.0	20.0	23.0	26.0
MEAN	115.3	37.0	62.0	51.0	38.7	35.7	34.7	30.7
(+/-SEM)	10.2	6.7	23.0	18.0	12.8	8.7	8.4	7.3

Table 4. PLASMA NOREPINEPHRINE (pg/ml) IN WOUNDED CATS

	CONT	1 MIN	3 MIN	5 MIN	10 MIN	20 MIN	30 MIN	60 MIN
CONTROLS								
CG12	955	881	992	970	862	708	1183	705
CG13	1550	1516	1409	1592	1483	1287	1394	1472
CG15	1293	1716	1374	1315	970	1788	1009	1028
MEAN	1266	1371	1258	1292	1105	1261	1195	1068
(+/-SEM)	172	252	134	180	192	312	111	222
0.9 JOULES								
CG7	1403	1598	1339	972	878	886	848	708
CG9	1310	1776	1551	1521	1516	1438	1302	1353
CG11	1396	2588	1880	1955	1442	1497	1556	1509
MEAN	1370	1987	1590	1482	1278	1273	1235	1190
(+/-SEM)	30	305	157	284	201	195	207	245
1.4 JOULES								
CG1	853	15636	6419	3116	2853	2426	1742	1634
CG14	1853	15687	3940	2663	1254	976	993	1329
CG17	770	5308	2342	2348	1787	1774	1831	879
MEAN	864	10046	3931	2418	1955	1569	1398	1049
(+/-SEM)	58	3012	1260	384	477	563	389	301
2.4 JOULES								
CG6	2899	5786	3179	2758	2837	2629	2570	2905
CG8	899	7841	3338	2373	1068	615	570	613
CG16	1219	12491	6126	4053	2388	1671	593	647
MEAN	1139	9506	4189	3171	2050	1404	1012	937
(+/-SEM)	122	1496	971	487	499	402	430	307

Table 5. PLASMA EPINEPHRINE (pg/ml) IN WOUNDED CATS

	CONT	1 MIN	3 MIN	5 MIN	10 MIN	20 MIN	30 MIN	60 MIN
CONTROLS								
CG12	75.0	71.0	90.0	88.0	80.0	114.0	111.0	103.0
CG13	89.0	65.0	99.0	91.0	67.0	106.0	96.0	76.0
CG15	87.0	74.0	134.0	167.0	172.0	124.0	29.0	204.0
MEAN	83.7	70.0	107.7	115.3	106.3	114.7	78.7	127.7
(+/-SEM)	4.4	2.6	13.4	25.8	33.0	5.2	25.2	39.0
0.9 JOULES								
CG7	56.0	2090.0	280.0	127.0	138.0	141.0	163.0	51.0
CG9	78.0	1108.0	266.0	215.0	222.0	240.0	262.0	152.0
CG11	77.0	569.0	118.0	132.0	82.0	102.0	77.0	94.0
MEAN	70.3	1255.7	221.3	158.0	147.3	161.0	167.3	99.0
(+/-SEM)	7.2	445.2	51.8	28.5	40.7	41.1	53.4	29.3
1.4 JOULES								
CG1	270.0	22864.0	8566.0	4224.0	5792.0	4445.0	3011.0	3142.0
CG14	68.0	20314.0	6099.0	2570.0	781.0	278.0	513.0	89.0
CG17	131.0	9997.0	4266.0	2999.0	3356.0	2821.0	2007.0	648.0
MEAN	158.3	17204.7	7184.7	3011.0	3355.7	2662.3	1882.0	1410.3
(+/-SEM)	58.2	3794.2	1460.0	696.9	1406.7	1077.9	690.7	867.9
2.4 JOULES								
CG6	89.0	8868.0	1635.0	1068.0	1028.0	759.0	878.0	1005.0
CG8	80.0	15900.0	6158.0	2110.0	1026.0	633.0	382.0	322.0
CG16	47.0	11415.0	6893.0	6799.0	5133.0	2228.0	896.0	703.0
MEAN	76.0	12286.3	4854.7	3313.7	2322.7	1123.0	540.3	383.0
(+/-SEM)	15.7	1885.8	1684.3	1770.2	1406.6	553.7	178.2	169.9

Table 6. PLASMA GLUCOSE IN WOUNDED CATS

	CONT	1 MIN	3 MIN	5 MIN	10 MIN	20 MIN	30 MIN	60 MIN
CONTROLS								
CG12	117.0	139.0	129.0	134.0	135.0	158.0	151.0	139.0
CG13	137.0	132.0	133.0	125.0	134.0	138.0	158.0	159.0
CG15	131.0	137.0	131.0	141.0	146.0	130.0	142.0	168.0
MEAN	128.3	136.0	131.0	133.3	138.3	142.0	150.3	155.3
(+/-SEM)	5.9	2.1	1.2	4.6	3.8	8.3	4.6	8.6
0.9 JOULES								
CG7	134.0	133.0	162.0	178.0	155.0	153.0	195.0	232.0
CG9	104.0	104.0	132.0	169.0	160.0	151.0	180.0	184.0
CG11	184.0	189.0	207.0	236.0	233.0	236.0	227.0	239.0
MEAN	142.3	154.0	167.0	194.3	182.7	180.0	200.7	218.3
(+/-SEM)	24.9	28.8	21.8	21.0	25.2	28.0	13.9	17.3
1.4 JOULES								
CG1	89.0	110.0	156.0	194.0	331.0	415.0	433.0	407.0
CG14	101.0	94.0	182.0	204.0	197.0	273.0	269.0	261.0
CG17	92.0	90.0	259.0	307.0	296.0	235.0	192.0	233.0
MEAN	98.0	120.3	199.0	235.0	274.7	307.7	298.0	300.3
(+/-SEM)	6.1	7.8	30.9	36.1	36.1	54.8	71.1	53.9
2.4 JOULE								
CG6	107.0	91.0	144.0	211.0	213.0	172.0	203.0	169.0
CG8	129.0	132.0	248.0	274.0	268.0	291.0	248.0	255.0
CG16	183.0	169.0	188.0	204.0	197.0	209.0	205.0	238.0
MEAN	131.0	150.0	193.3	229.7	226.0	224.0	218.7	220.7
(+/-SEM)	22.5	18.3	30.1	22.3	21.5	35.2	14.7	26.3

PART 2. ARTIFICIALLY INCREASING ICP TO 80 torr BY INFUSING MOCK CSF OVER THE RIGHT CEREBRAL HEMISPHERE (LATERAL OR ASYMMETRIC LOAD)

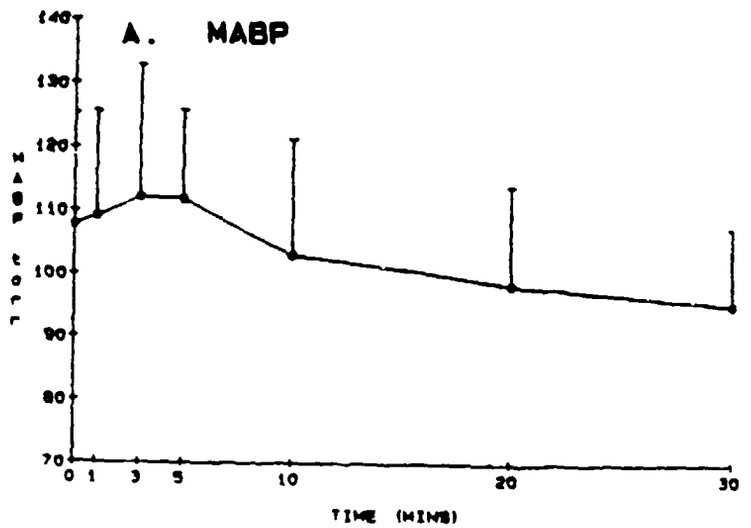
In order to determine if the physiological and/or biochemical responses seen in the injury could be solely or partially attributable to an increase in ICP alone, additional experiments were performed. Since our injury model places a large ASYMETRIC load on one side (right) of the brain, we placed a small hole in the right side of the skull and applied a fluid column (mock CSF) in order to adjust the ICP levels. The ICP was raised very rapidly (approx. 30s) for 2.5 mins., then decreased to 40 torr until 20 mins., then the column was disconnected , allowing a normal ICP to be reestablished. This time frame closely mimics the ICP response of our injured animals (see 1986-1987 yearly report). Blood samples were collected at 1, 3, 5, 10, 20 and 30 mins. Since we were only interested in the immediate responses, the 60 min. sample was excluded.

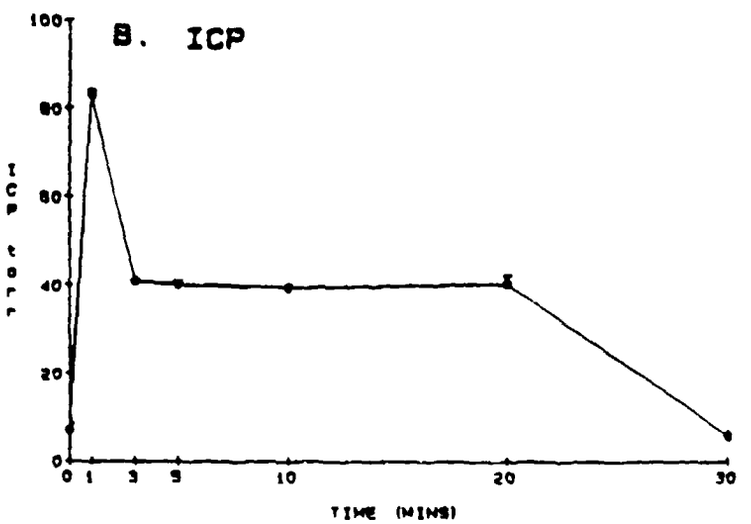
RESULTS

As can be seen in table 7 and fig. 11A-F, this manipulation resulted in an immediate increase in ICP, however there were no increases in MABP at any time point although the CPP was significantly depressed until 20 min. Likewise, there were no significant effects on plasma EPI or glucose. Plasma NE, however, did exhibit a late rise at 30 min.

This experiment demonstrated that raising the ICP to 80 torr by a lateral extradural load alone did NOT have the same effects on the plasma CA response as the brain wound.

Fig 11 (A-F). PHYSIOLOGICAL AND BIOCHEMICAL RESULTS WHEN ICP IS ELEVATED TO 80 torr BY A LATERAL LOAD





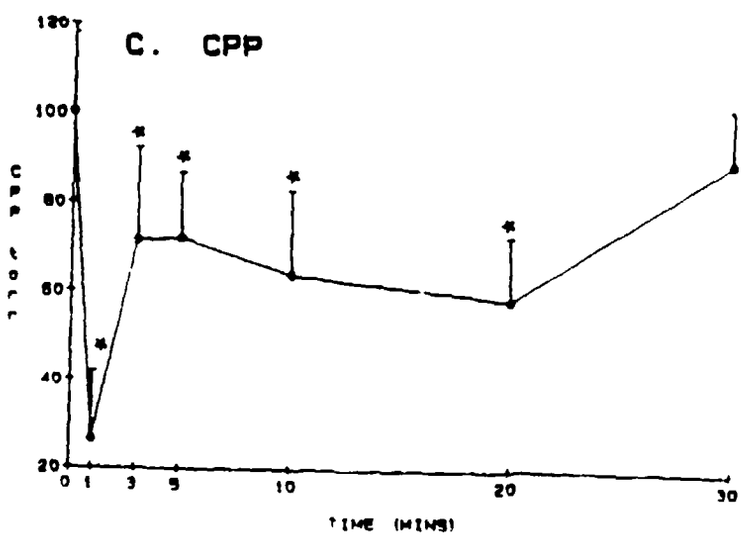


Fig 11. (cont'd)

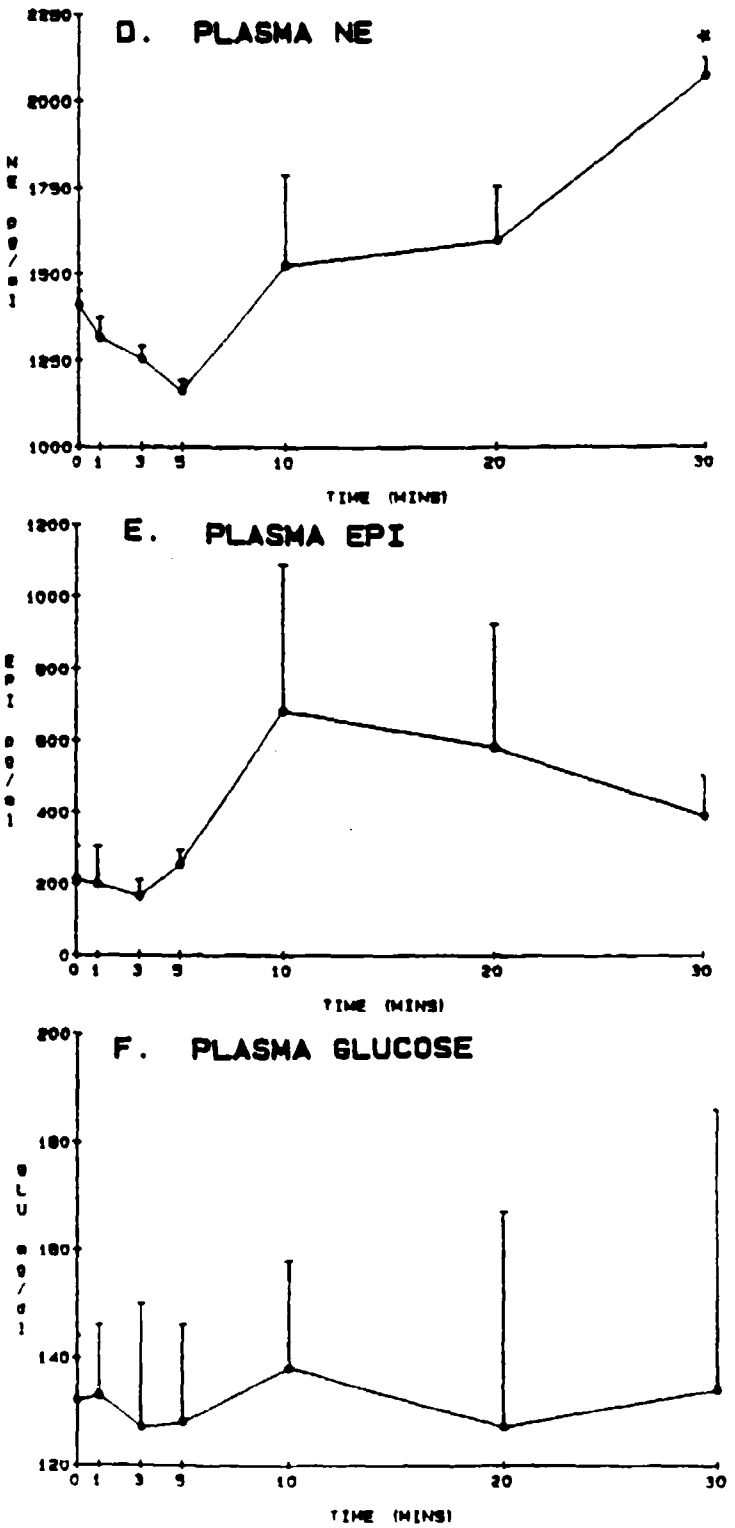

D. PLASMA NE
NE pg/ml
2250
2000
1750
1500
1250
1000
0 1 3 5 10 20 30
TIME (MINS)
E. PLASMA EPI
EPI pg/ml
1200
1000
800
600
400
200
0
0 1 3 5 10 20 30
TIME (MINS)
F. PLASMA GLUCOSE
GLU mg/dl
200
180
160
140
120
0 1 3 5 10 20 30
TIME (MINS)

Table 7. PHYSIOLOGICAL AND BIOCHEMICAL RESULTS WHEN ICP IS ELEVATED TO 80 torr BY A LATERAL LOAD

	CONT	1 MIN	3 MIN	5 MIN	10 MIN	20 MIN	30 MIN
MABP							
CG22	140.0	140.0	153.0	137.0	137.0	127.0	118.0
CG23	80.0	84.0	87.0	89.0	74.0	73.0	76.0
CG24	103.0	103.3	96.0	109.0	98.0	95.0	92.0
MEAN	107.7	109.0	112.0	111.7	103.0	98.3	95.3
(+/-SEM)	17.5	16.4	20.7	13.9	18.4	15.7	12.2
ICP							
CG22	6.0	84.0	40.0	38.0	38.0	44.0	6.0
CG23	10.0	80.0	42.0	41.0	40.0	40.0	6.0
CG24	5.0	84.0	40.0	41.0	40.0	37.0	5.0
MEAN	7.0	82.7	40.7	40.0	39.3	40.3	5.7
(+/-SEM)	1.5	1.3	0.7	1.0	0.7	2.0	0.3
CPP							
CG22	132.0	56.0	113.0	99.0	99.0	83.0	112.0
CG23	70.0	4.0	45.0	48.0	34.0	33.0	70.0
CG24	98.0	19.0	56.0	68.0	58.0	58.0	87.0
MEAN	100.0	26.3	71.3	71.7	63.7	58.0	89.7
(+/-SEM)	17.9	15.5	21.0	14.8	19.0	14.4	12.2
NE							
CG22	1439.0	1338.0	1282.0	1223.0	2050.0	1836.0	2035.0
CG23	1460.0	1208.0	1300.0	1155.0	1239.0	1300.0	2178.0
CG24	1327.0	1401.0	1181.0	1108.0	1282.0	1650.0	2000.0
MEAN	1409.0	1316.0	1254.0	1162.0	1524.0	1595.0	2071.0
(+/-SEM)	41.0	57.0	37.0	33.0	263.0	157.0	54.0
EPI							
CG22	162.0	130.0	185.0	144.0	441.0	302.0	560.0
CG23	393.0	409.0	232.0	533.0	1478.0	1266.0	432.0
CG24	88.0	57.0	75.0	81.0	127.0	172.0	170.0
MEAN	214.0	199.0	164.0	253.0	682.0	580.0	387.0
(+/-SEM)	92.0	107.0	47.0	41.0	408.0	345.0	115.0
GLUCOSE							
CG22	151.0	152.0	172.0	163.0	174.0	191.0	223.0
CG23	137.0	137.0	108.0	116.0	135.0	136.0	137.0
CG24	109.0	109.0	101.0	106.0	106.0	54.0	43.0
MEAN	132.0	133.0	127.0	128.0	138.0	127.0	134.0
(+/-SEM)	12.0	13.0	23.0	18.0	20.0	40.0	52.0

PART 3. ARTIFICIALLY INCREASING ICP TO 80 torr BY MOCK CSF INFUSION INTO THE CISTERNA MAGNA (SYMMETRIC LOAD)

The second approach to artificially increasing ICP without injury was to insert a 20ga. needle into the cisterna magna and attach it to the aforementioned fluid column. This has the effect of producing a large SYMMETRIC load on the brain. The same blood sampling protocol was used as previously described.

RESULTS

Utilizing this methodology the physiological and biochemical responses were variable; thus individual and not group data are presented in table 8 and fig.12A-F. Despite the very rapid rise in ICP to 80 torr only two animals (CG-17 and CG-20) exhibited a rise in MABP. Plasma CA levels increased in the same animals which showed MABP elevations (CG-17 and CG-20). In CG-17 the plasma CA and MABP elevations did not occur until 5 and 10 mins., respectively, postinjury. Animal CG-20 showed IMMEDIATE rises in both plasma CAs and MABP.

The significance of these results is that only two of four animals displayed increases in MABP and plasma CAs. Thus only one of four cases mimicked an injured animal. Therefore, increasing ICP to 80 torr by either an asymetric or symmetric load did not convincingly elicit a plasma CA response similar to that seen following a missile wound to the brain.

Fig 12 (A-F). PHYSIOLOGICAL AND BIOCHEMICAL RESULTS WHEN ICP IS ELEVATED TO 80 torr BY MOCK CSF INFUSION INTO THE CISTERNA MAGNA

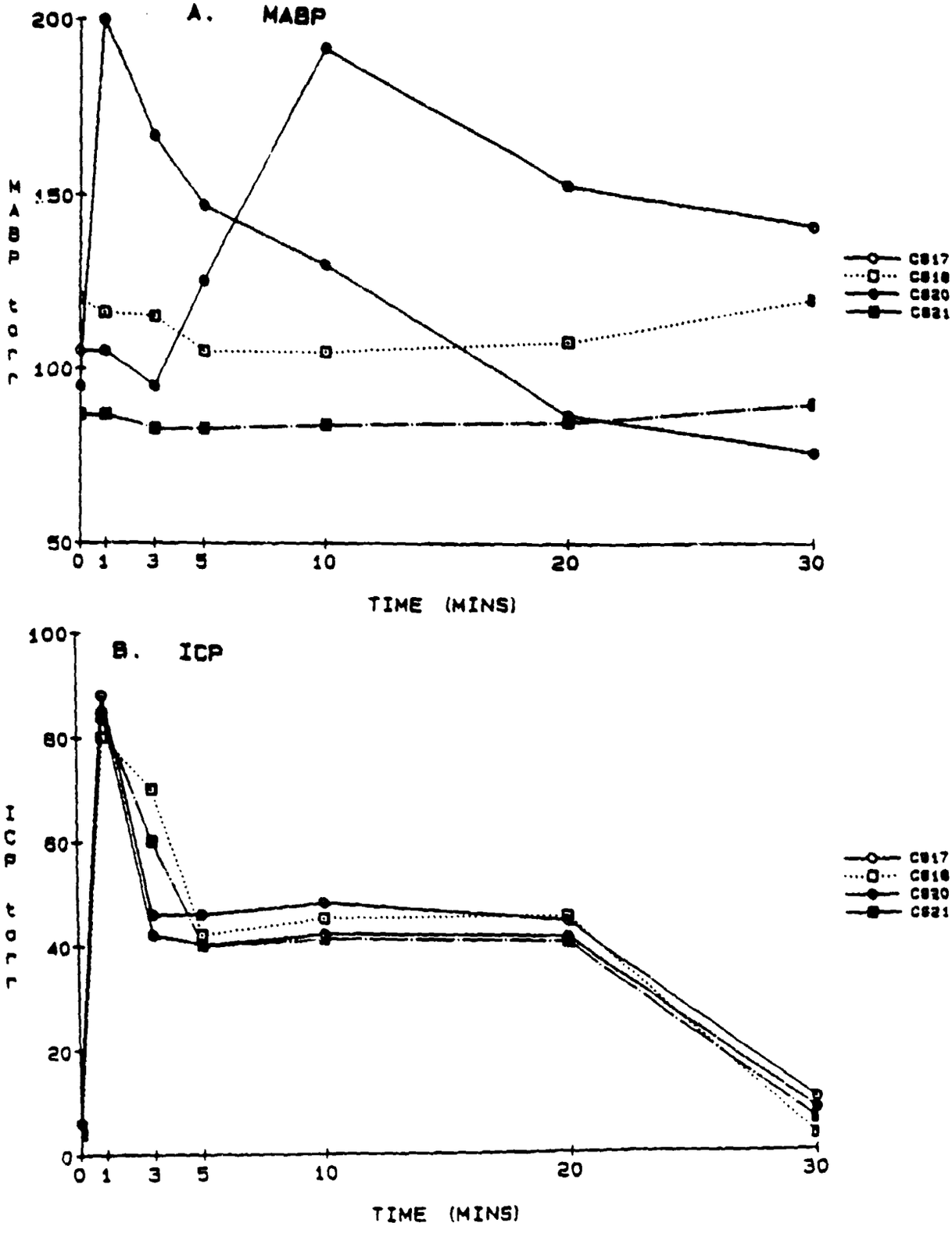
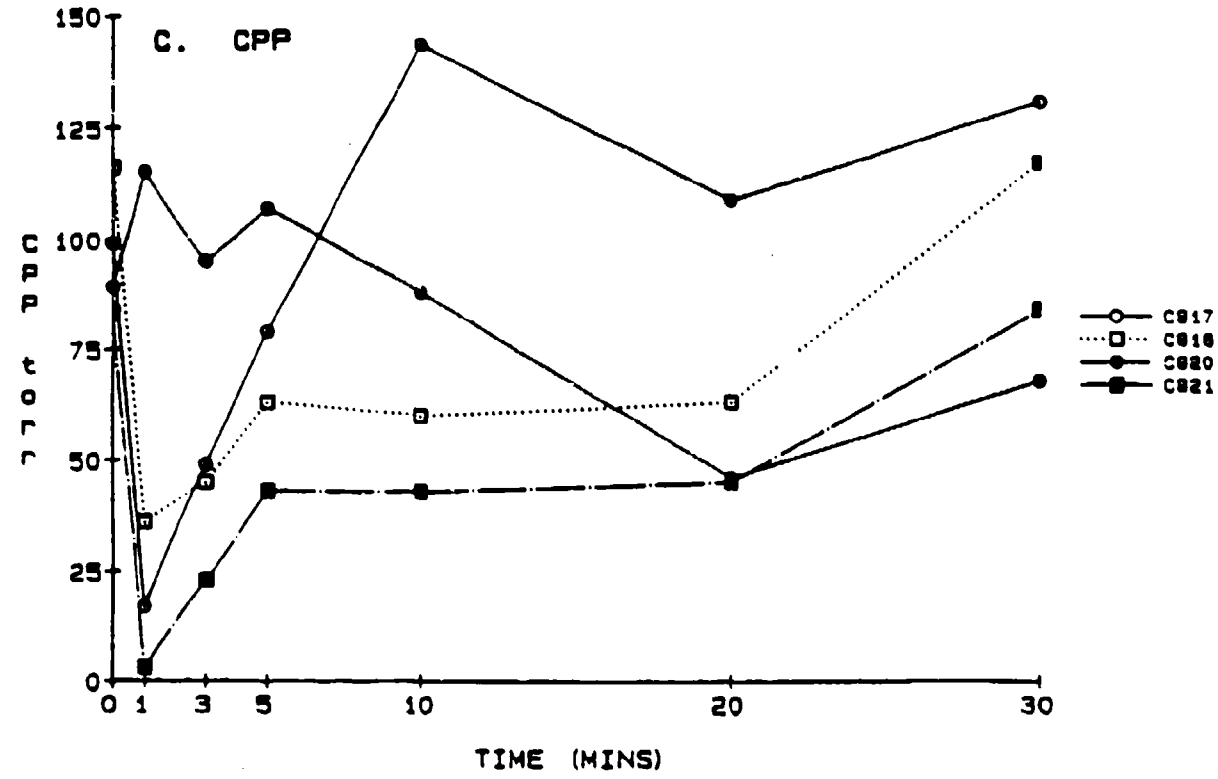


Fig 12. (cont'd)


C. CPP
CPP (mm Hg)
150
125
100
75
50
25
0
0 1 3 5 10 20 30
TIME (MINS)
C017
C018
C020
C021

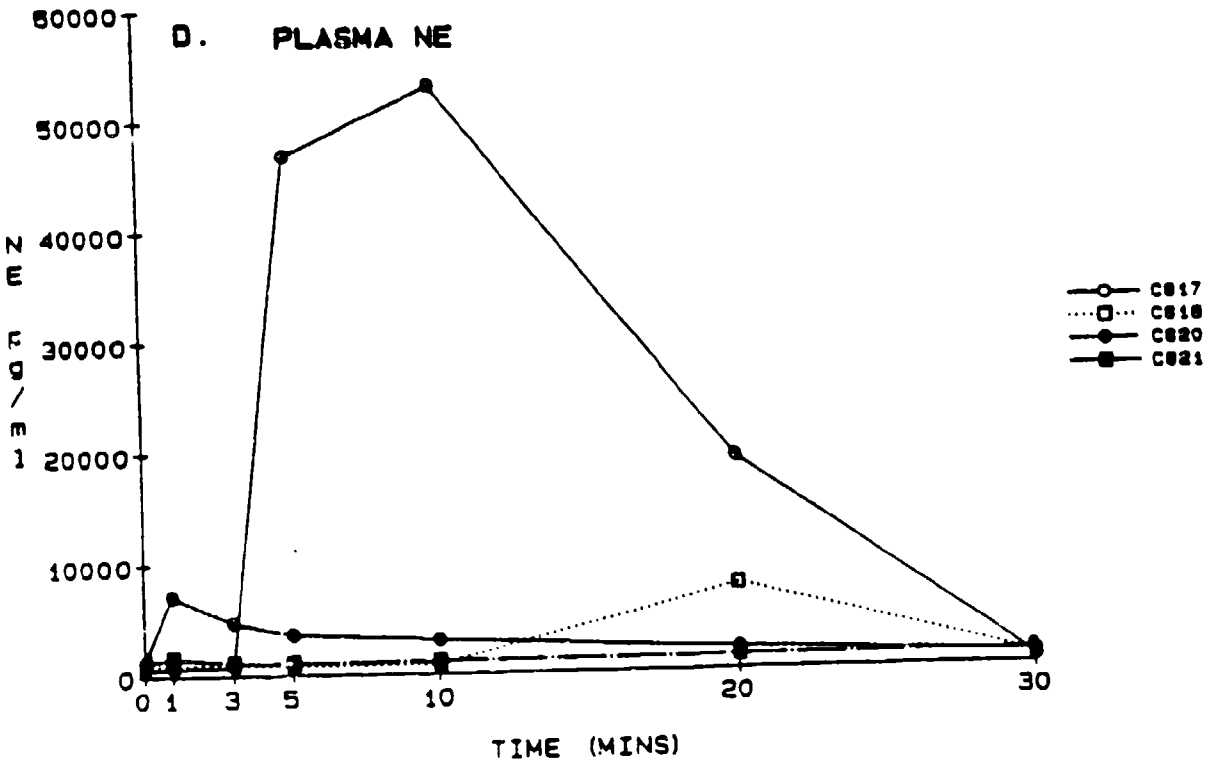
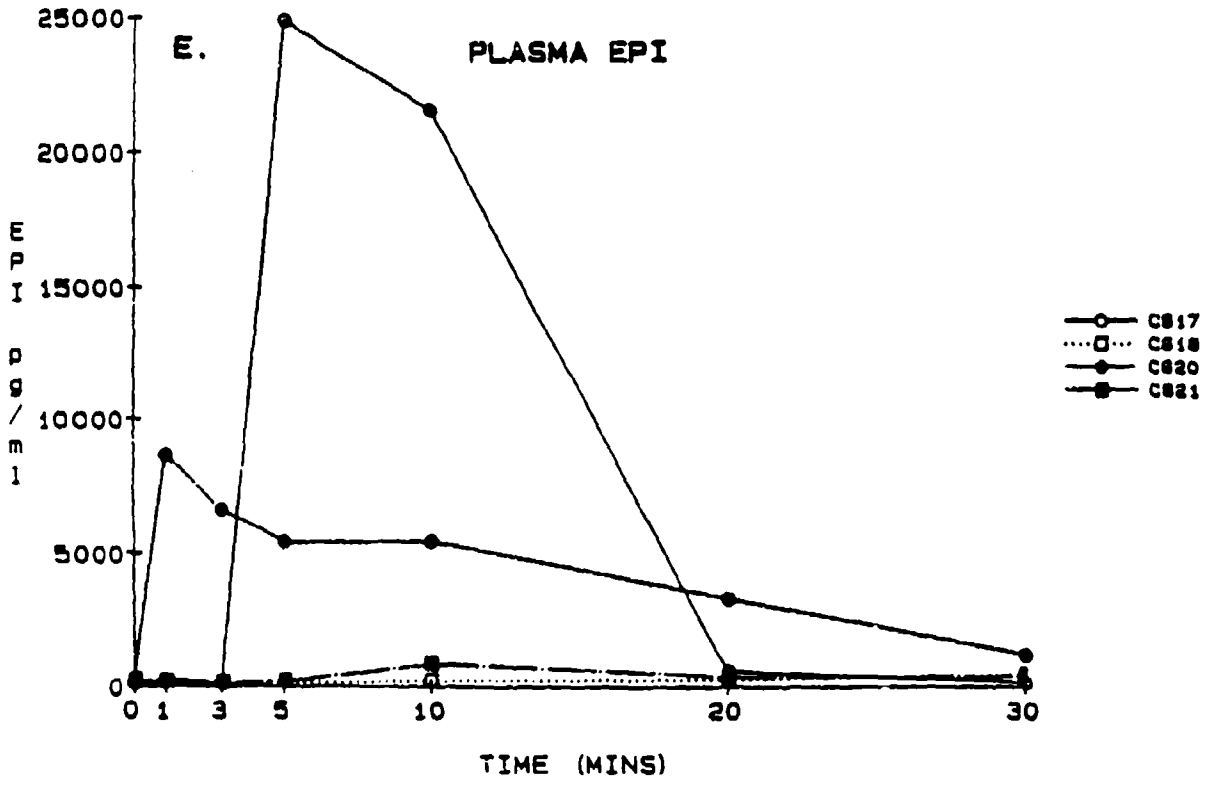

D. PLASMA NE
NE (pg/ml)
60000
50000
40000
30000
20000
10000
0
0 1 3 5 10 20 30
TIME (MINS)
C017
C018
C020
C021

Fig 12. (cont'd)


E.
PLASMA EPI
25000
20000
15000
10000
5000
0
EPI pg/ml
0 1 3 5 10 20 30
TIME (MINS)
C817
C818
C820
C821

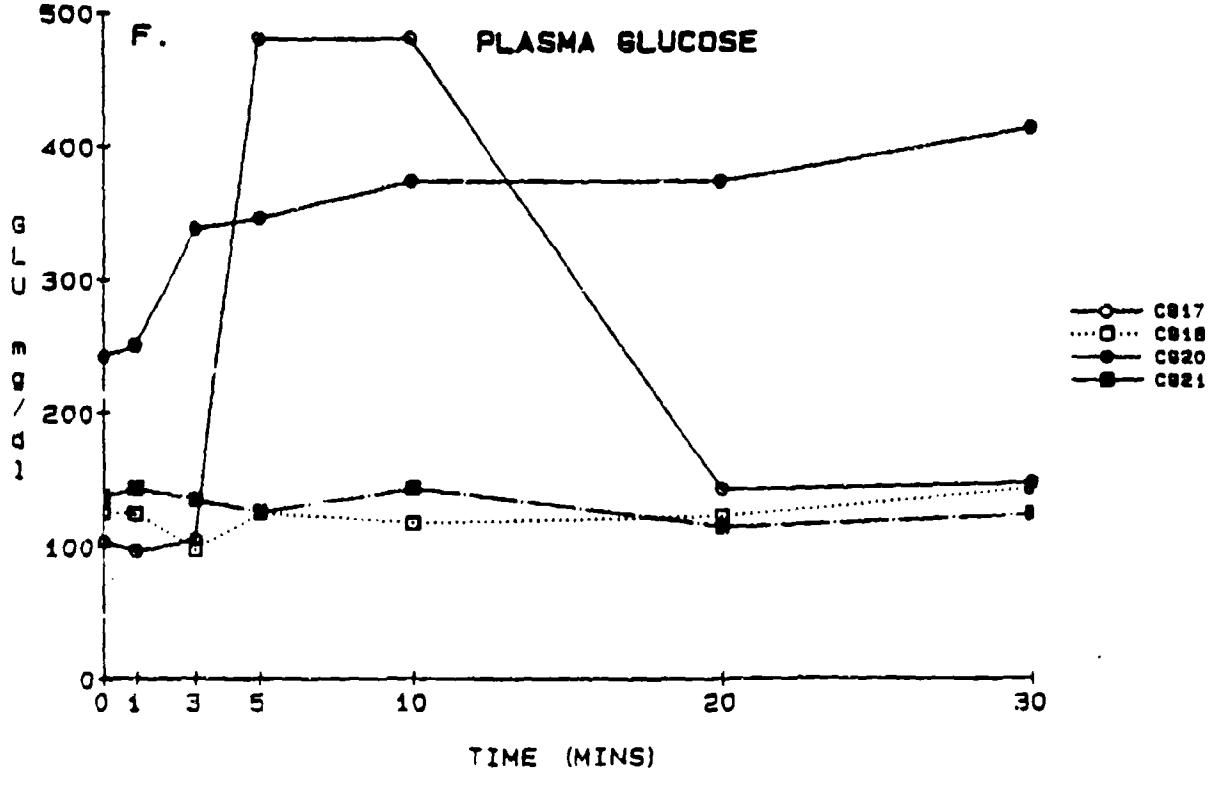

F.
PLASMA GLUCOSE
500
400
300
200
100
0
GLU mg/dl
0 1 3 5 10 20 30
TIME (MINS)
C817
C818
C820
C821

Table 8. PHYSIOLOGICAL AND BIOCHEMICAL RESULTS WHEN ICP IS ELEVATED TO 80 torr BY MOCK CSF INFUSION INTO THE CISTERNA MAGNA

	CONT	1 MIN	3 MIN	5 MIN	10 MIN	20 MIN	30 MIN
MABP							
CG17	105	105	95	125	192	153	141
CG18	120	116	115	105	105	108	120
CG20	95	200	167	147	130	87	76
CG21	87	87	83	83	84	85	90
ICP							
CG17	6	88	46	46	48	44	10
CG18	4	80	70	42	45	45	3
CG20	6	85	42	40	42	41	8
CG21	4	84	60	40	41	40	6
CPP							
CG17	99	17	49	79	144	109	131
CG18	116	36	45	63	60	63	117
CG20	89	115	95	107	88	46	68
CG21	83	3	23	43	43	45	84
NE							
CG17	611	753	762	46928	53176	19106	575
CG18	958	1023	943	855	867	7626	859
CG20	1152	7125	4680	3566	3037	1871	1035
CG21	1301	1587	1091	1086	1148	1201	1280
EPI							
CG17	135	254	103	24883	21597	608	154
CG18	249	199	181	140	219	274	460
CG20	312	8661	6630	5417	5455	3328	1195
CG21	133	92	112	192	854	387	407
GLU							
CG17	103	96	105	480	481	142	147
CG18	125	124	97	124	117	122	143
CG20	242	250	338	346	374	374	413
CG21	137	143	134	125	143	114	123

PART 4. ARTIFICIALLY INCREASING ICP TO 150 torr BY MOCK CSF INFUSION INTO THE CISTERNA MAGNA (SYMMETRIC LOAD)

These experiments were conducted exactly as the previous ones except that the ICP was rapidly raised to 150 torr to determine if a further increase in ICP would have different effects on the physiological and biochemical responses.

RESULTS

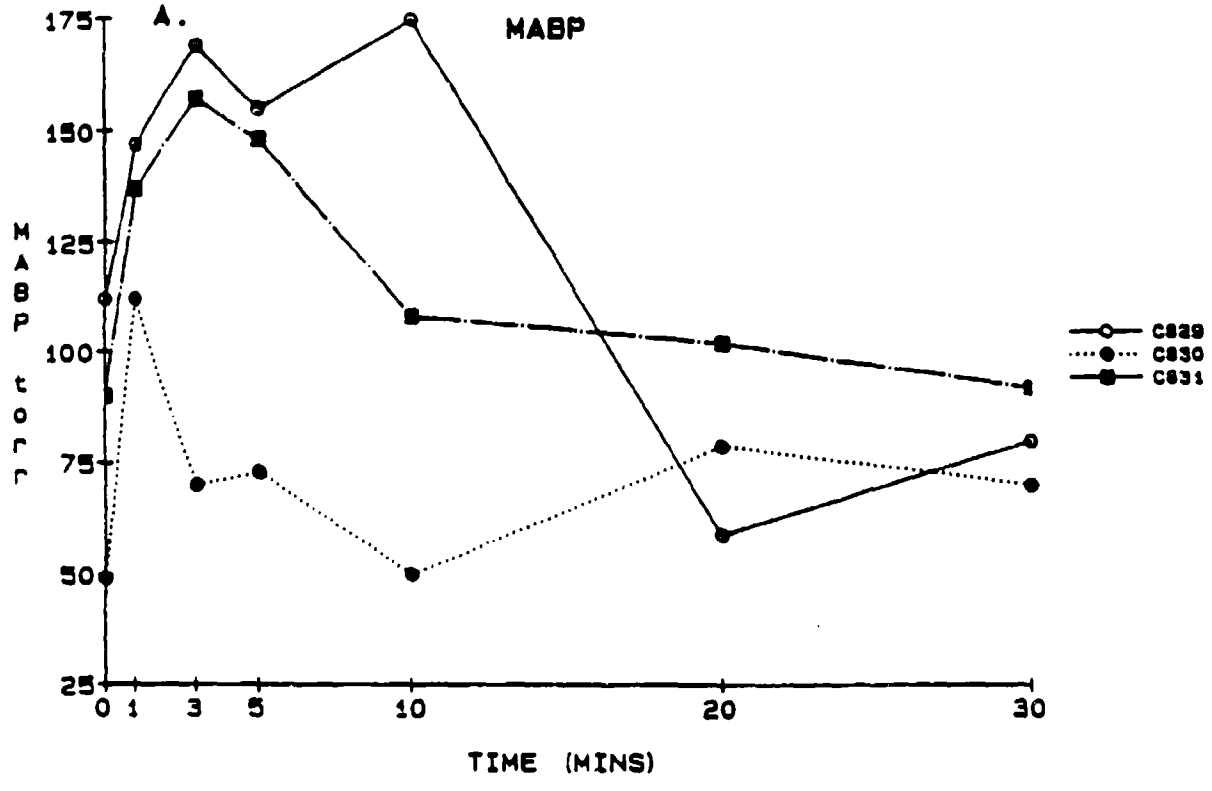
All three cats in this group, (CG-29, CG-30, CG-31), exhibited immediate (1-3 min) MABP increases in response to increased ICP and decreased CPP. CG-29 displayed increases in plasma NE and EPI at 3, 5 and 10 mins., while CG-30 exhibited increases in plasma NE and EPI at 3 mins. However, CG-31 displayed no increases in plasma NE or EPI even though the MABP was elevated (table 9, fig.13A-F). This was the only case out of thirty one where an increase in MABP was not accompanied by an increase in plasma CAs. This was not an assay problem because there was NO rise in glucose levels , as with CG-29 and CG-30 and all other cases where significant elevations of plasma CAs were seen.

These experiments demonstrated that even raising the ICP to 150 torr did NOT result in an IMMEDIATE increase in plasma CAs seen in all cases of missile wounds to the brain. Rather, any plasma CA responses which did occur were delayed from 3 to 10 mins.

DISCUSSION

From the three sets of experiments (total N=10) where the ICP was artificially increased utilizing a fluid column, there were only four cases in which there was an immediate increase in MABP in response to increased ICP. In three of the four cases this occurred only with an ICP of approx 150 torr and none of these three cases showed immediate increases in plasma CAs. Rather, plasma CA elevations in these animals were delayed. Therefore, there is only one case out of ten (PART 3., case CG-20) which exhibited both an immediate increase in MABP and plasma CAs. It seems likely, therefore, that in a large majority of the cases there will not be an immediate increase in plasma CAs in response to increased ICP alone. This observation is supported by others (5) and suggests that the immediate plasma CA rise with ICP elevations is at least partially due to other factors e.g. brainstem distortion.

Fig 13 (A-F). PHYSIOLOGICAL AND BIOCHEMICAL RESULTS WHEN ICP IS ELEVATED TO 150 torr BY MOCK CSF INFUSION INTO THE CISTERNA MAGNA



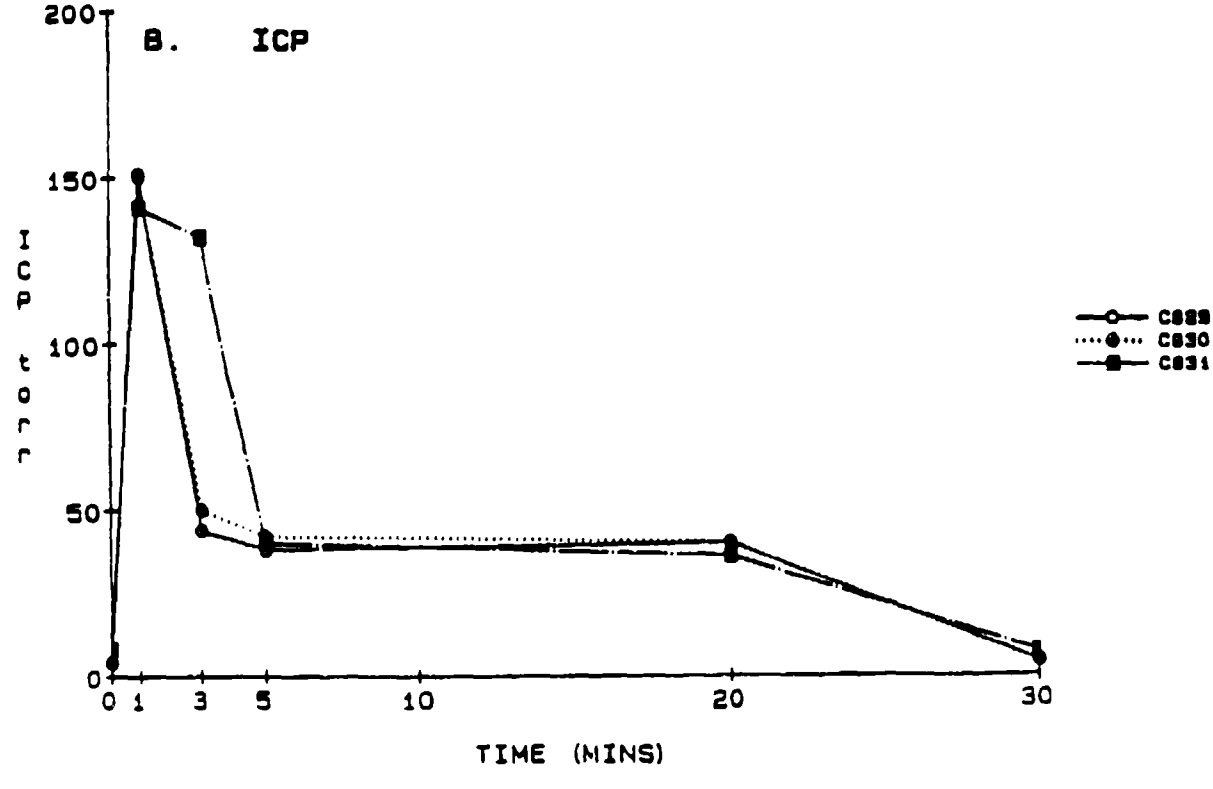
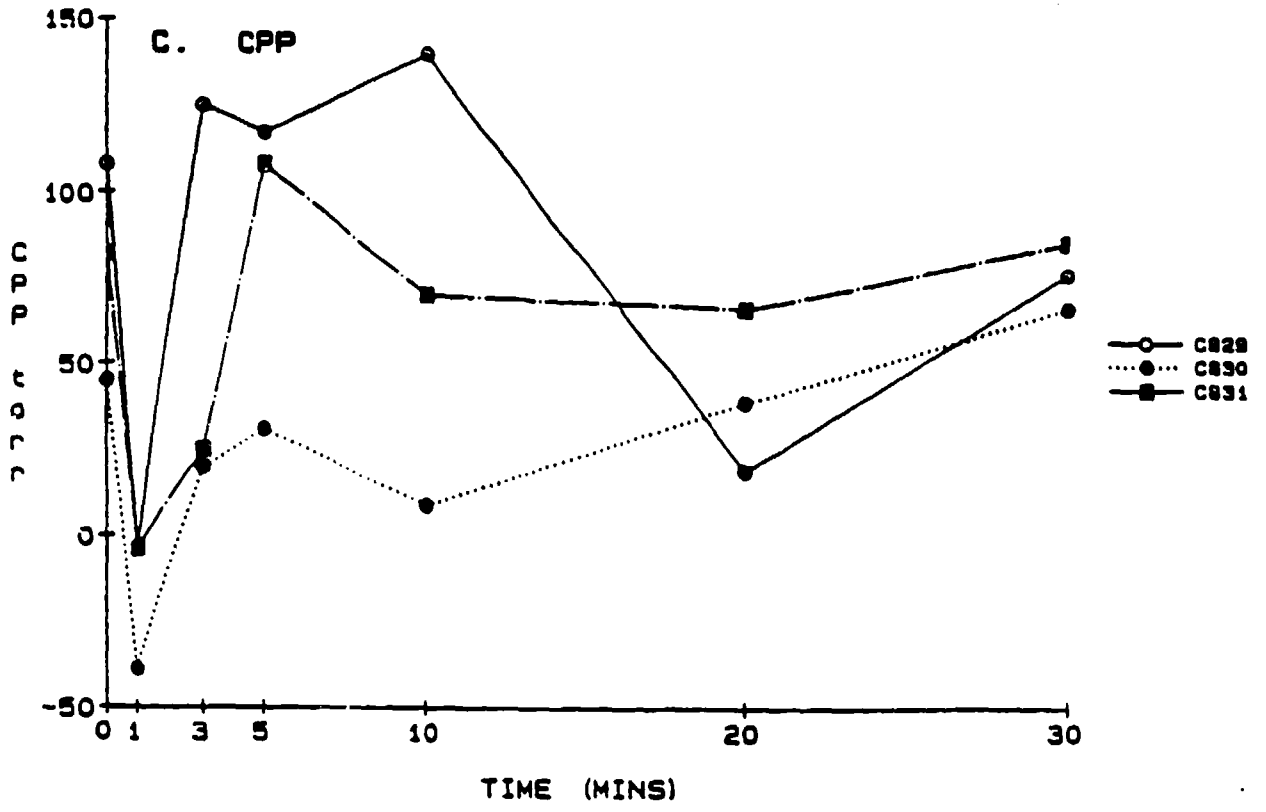


Fig 13. (cont'd)


C. CPP
150
100
50
0
-50
CPP cpcc
0 1 3 5 10 20 30
TIME (MINS)
C829
C830
C831

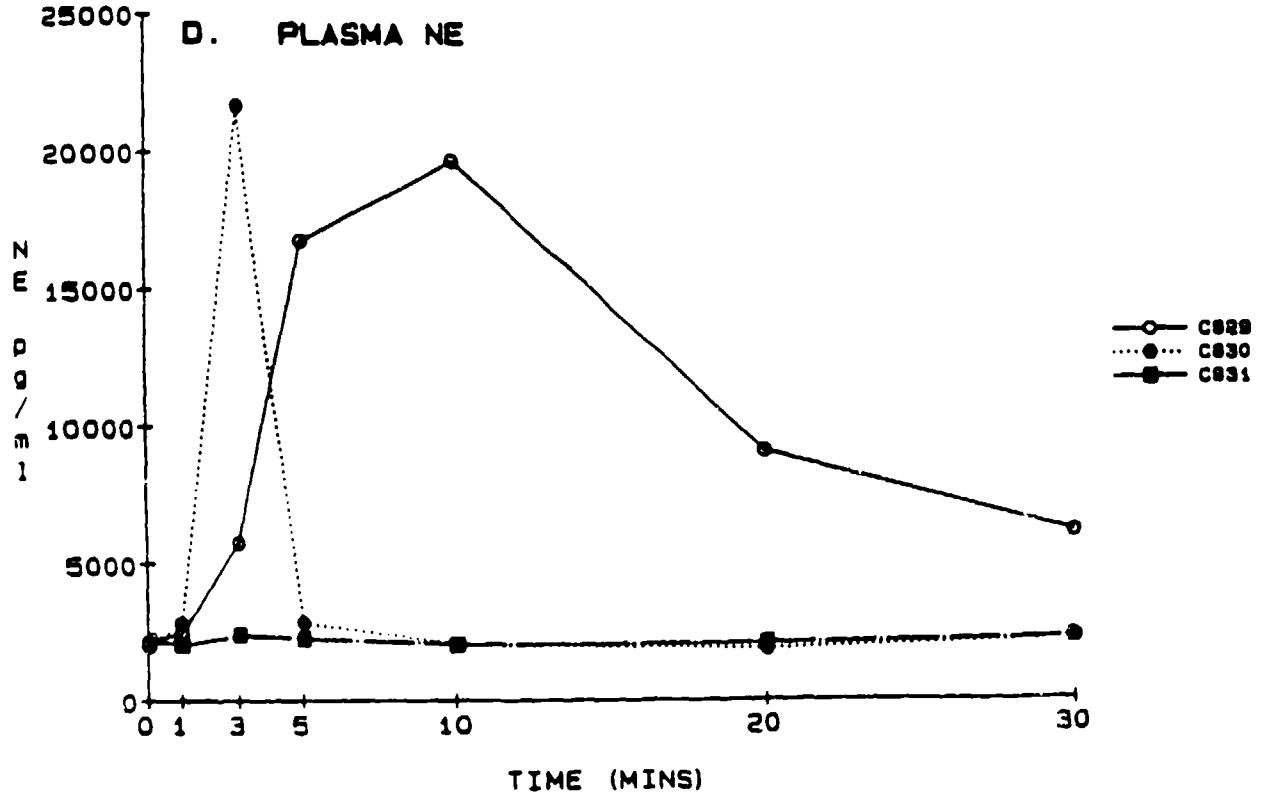
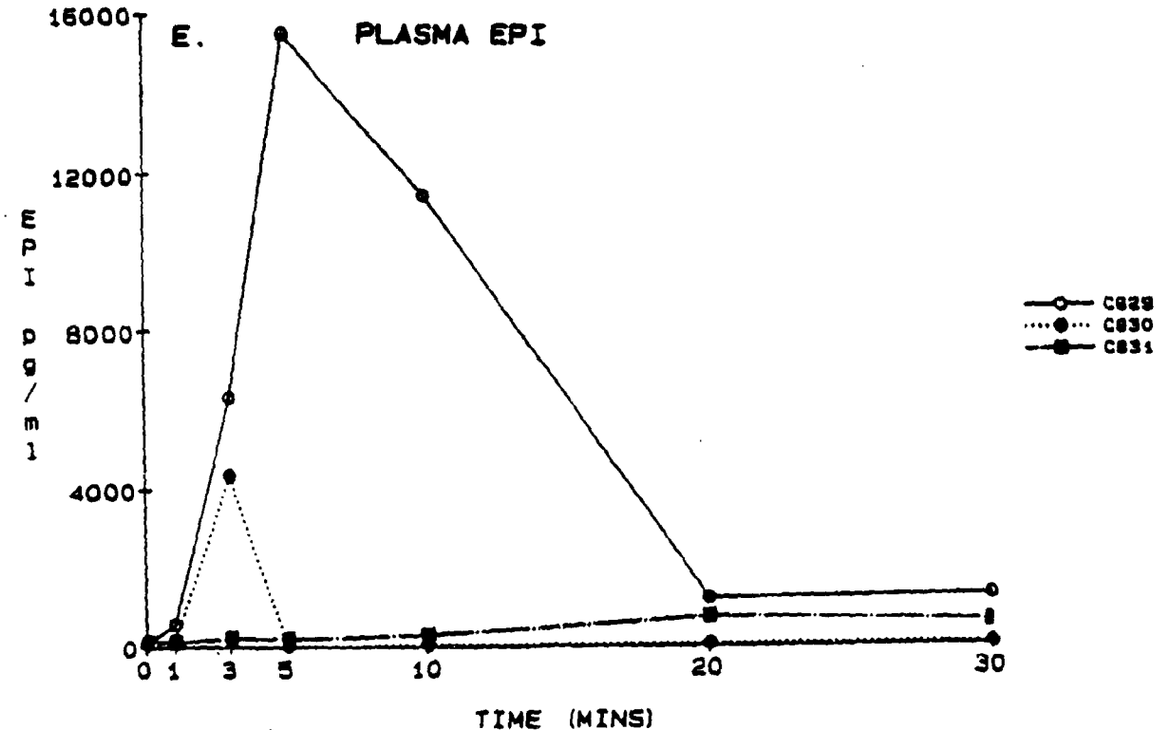

D. PLASMA NE
25000
20000
15000
10000
5000
0
NE pg/ml
0 1 3 5 10 20 30
TIME (MINS)
C829
C830
C831

Fig 13. (cont'd)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12000
8000
4000
0
EPI pg/ml
0 1 3 5 10 20 30
TIME (MINS)
C029
C030
C031

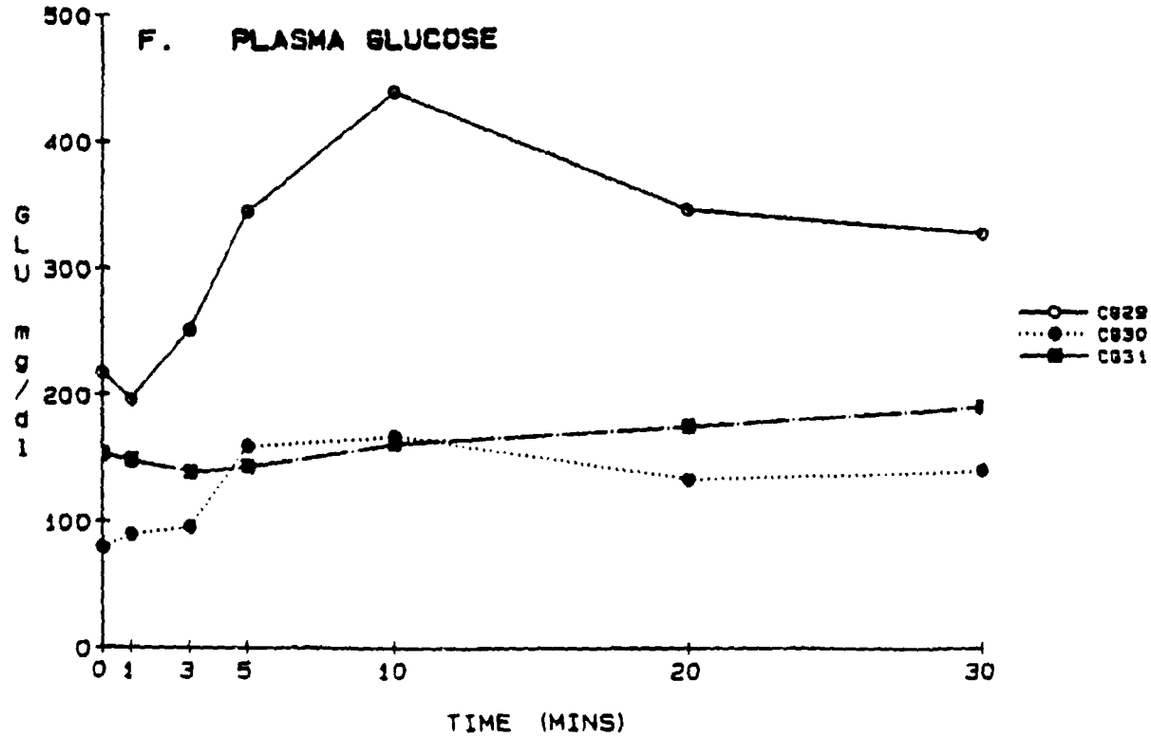

F. PLASMA GLUCOSE
500
400
300
200
100
0
GLU mg/dl
0 1 3 5 10 20 30
TIME (MINS)
C029
C030
C031

Table 9. PHYSIOLOGICAL AND BIOCHEMICAL RESULTS WHEN ICP IS ELEVATED TO 150 torr BY MOCK CSF INFUSION INTO THE CISTERNA MAGNA

	CONT	1 MIN	3 MIN	5 MIN	10 MIN	20 MIN	30 MIN
MABP							
CG29	112	147	169	153	175	59	80
CG30	49	112	70	73	50	79	70
CG31	90	137	157	148	108	102	92
ICP							
CG29	4	150	44	38	35	40	4
CG30	4	151	50	42	41	40	4
CG31	8	141	132	40	38	36	7
CPP							
CG29	108	-3	125	117	140	19	76
CG30	45	-39	20	31	9	39	66
CG31	82	-4	25	108	70	66	85
NE							
CG29	2128	2456	5729	16726	19598	9045	6078
CG30	1987	2766	2164	2820	2008	1833	2243
CG31	2168	2007	2365	2233	2019	2052	2261
EPI							
CG29	90	565	6341	15505	11415	1207	1277
CG30	129	163	4364	34	40	50	61
CG31	124	122	220	199	301	739	595
GLU							
CG29	217	196	251	345	440	347	328
CG30	79	89	95	159	167	133	140
CG31	153	148	138	143	161	175	191

PART 5. EFFECTS OF CHANGING TRAJECTORY ANGLE

In an effort to determine if the trajectory angle has an influence on the time course of the physiological and/or biochemical parameters, the trajectory was altered so as to injure the animal transversely across the frontal lobes. This angle avoids brain areas central to the sympathoadrenal response (eg. hypothalamus) and might put less force on the brainstem than the AP trajectory in which the missile impacts in the occipital and temporal regions near the brainstem. These experiments were accomplished by excising the temporal muscles on the right side of the head, decreasing the skull thickness to approximately 1 mm. in the target area and using a 2.4J energy shot. Blood samples were collected as previously described.

RESULTS

Four cases were tested and of these, two cats (CG-27 and CG-28), exhibited immediate rises in plasma CAs after wounding while two (CG-25 and CG-26) did not. CG-25 and CG-26 had ICPs of 38 and 73 respectively. Neither demonstrated immediate postwounding effects on MABP, plasma NE or EPI, but CG-25 did have a rise in plasma NE at 30 mins. Cases CG-27 and CG-28 had large increases in ICP immediately after wounding (152 and 153 torr respectively) and corresponding immediate increases in MABP, plasma NE and EPI and later rises in plasma glucose. Case CG-28 had an additional delayed increase in plasma NE and EPI at 20 min., while case CG-27 also began to show an additional secondary increase at 30 min.(table 10, fig.14A-F).

These experiments suggest that both the AP and transverse trajectories may cause some similar effects: both may cause an IMMEDIATE post-injury increase in MABP. In these instances there is also an IMMEDIATE significant rise in plasma CAs. Thus the immediate plasma CA elevations in animals sustaining a missile wound to the brain can be contrasted to the DELAYED plasma CA elevations seen in uninjured animals with an increased ICP.

The transverse trajectory appears to have a different effect on MABP and plasma CA responses than does the AP trajectory because only two of four transversely injured animals responded with elevations in MABP and plasma CAs, while nine of nine AP injured animals responded immediately. The two (CG-25 and CG-26) transversely injured animals not responding with elevations in MABP or plasma CAs had ICPs of 38 and 73 torr respectively. These are in marked contrast to those animals injured with an AP trajectory at 0.9J. These cats displayed immediate increases in MABP and the plasma CAs even though the ICP rose only to 18 TORR ! This may mean that the direction of the forces applied to the brainstem may be significant. It may take more force from a side trajectory to effect the same brain stem sympathetic response irrespective of any ICP increase.
(Recall that artifically raising the ICP to 80 torr had no effect whatsoever in six of the seven cases).

Fig 14 (A-F) . PHYSIOLOGICAL AND BIOCHEMICAL RESULTS WHEN WOUNDED USING A TRANSVERSE TRAJECTORY

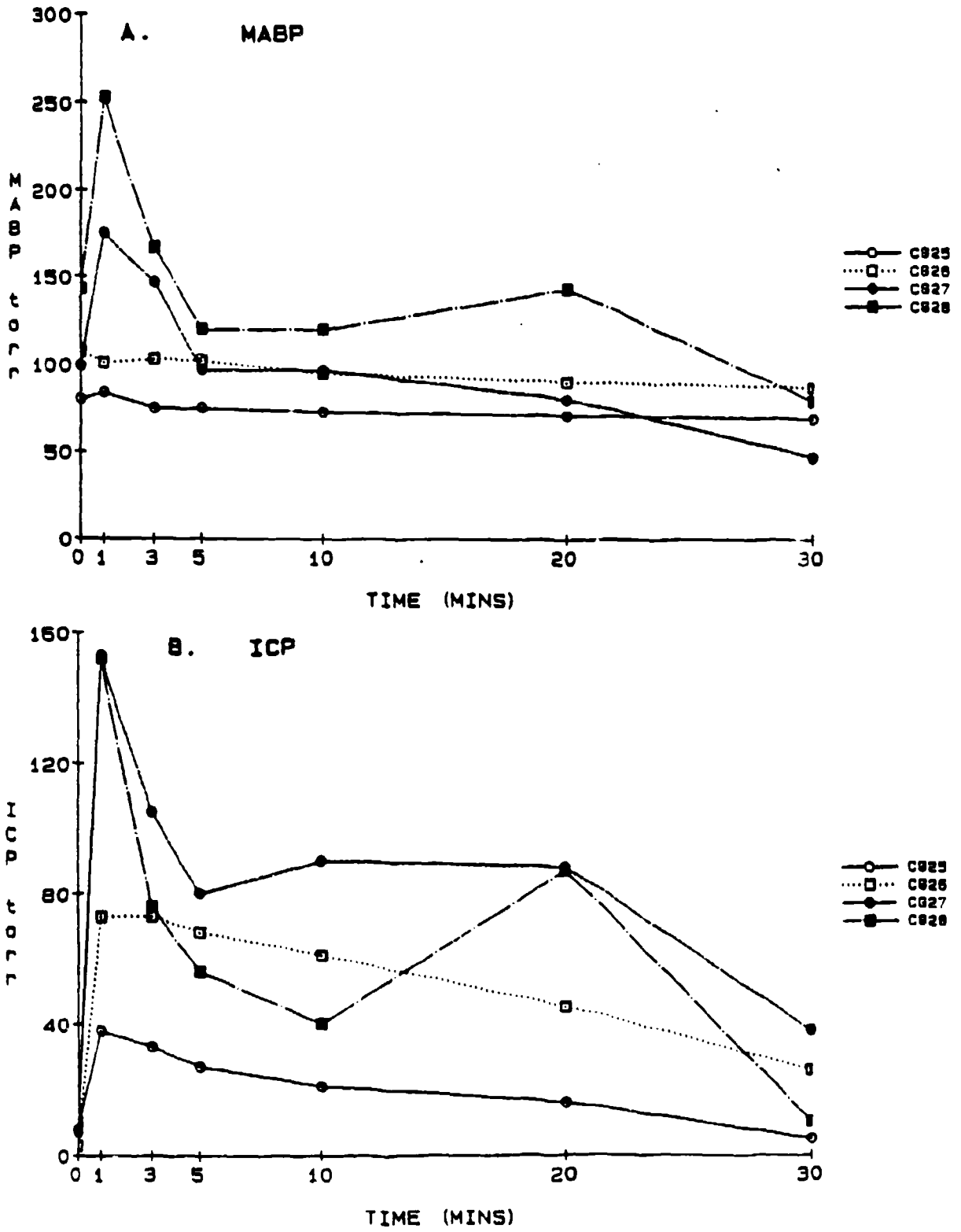
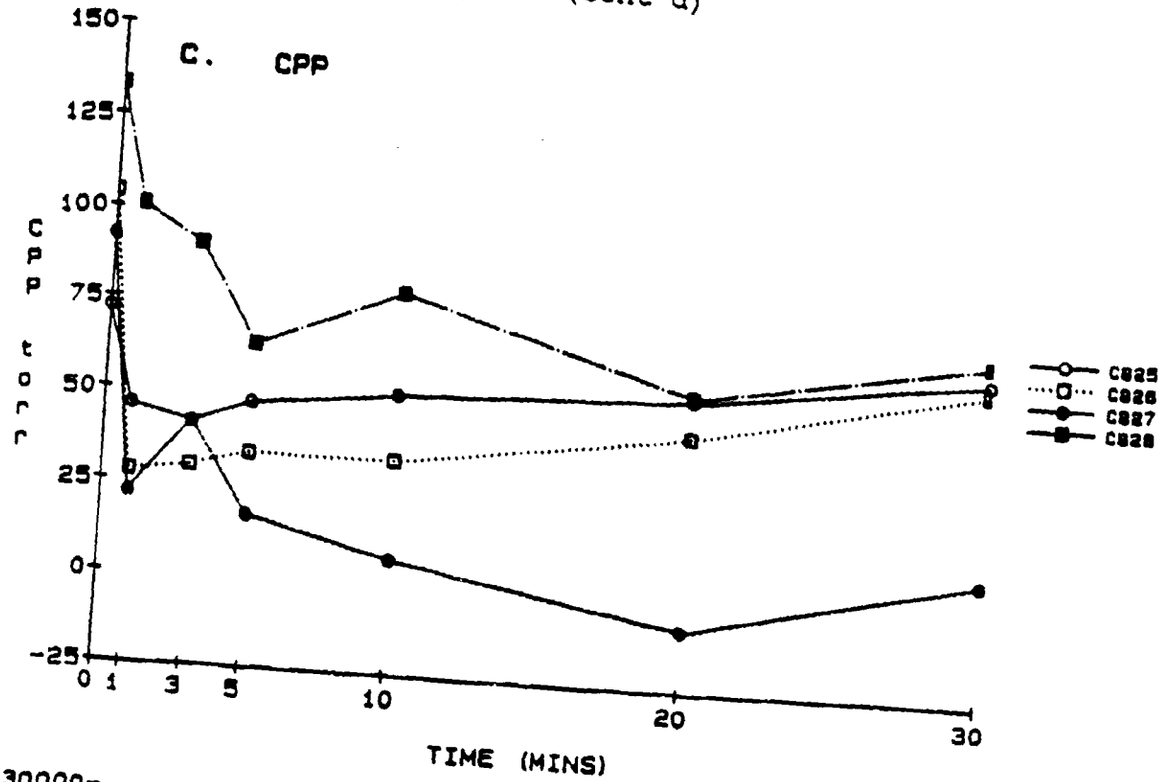


Fig 14. (cont'd)


C. CPP
150
125
100
75
50
25
0
-25
C P P t o r r
0 1 3 5 10 20 30
TIME (MINS)
C025
C026
C027
C028

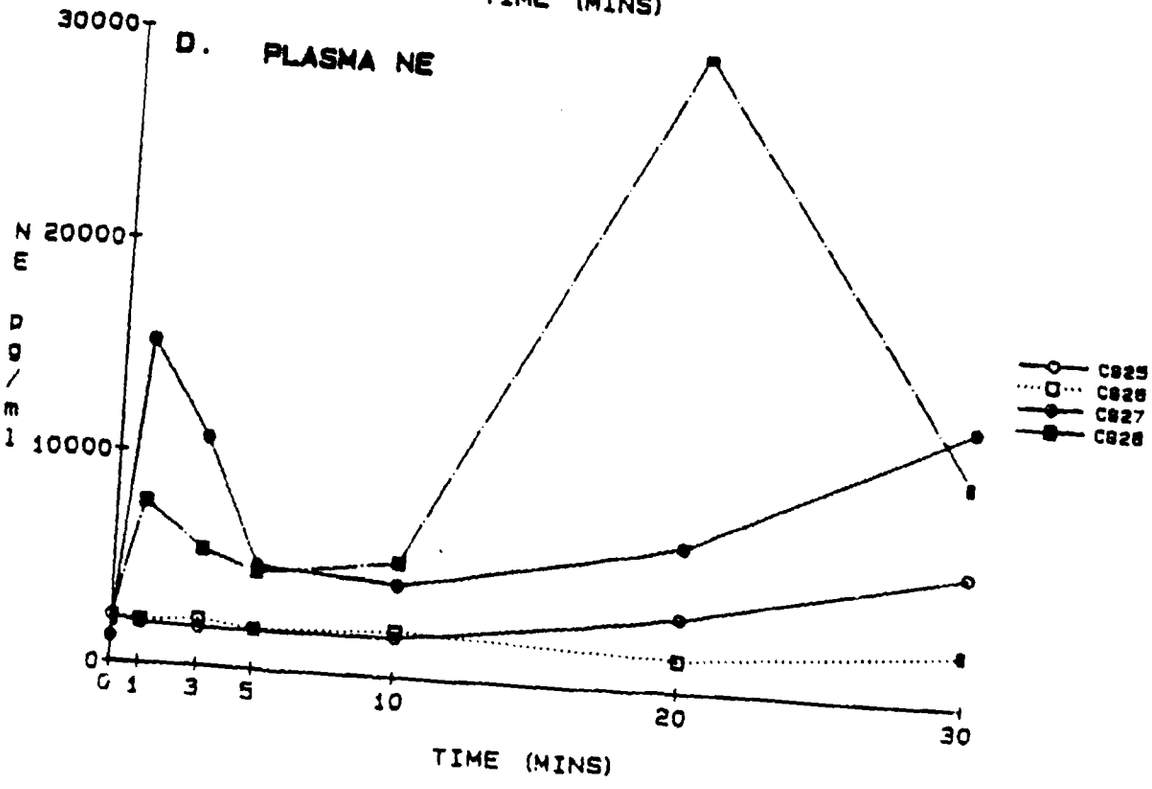
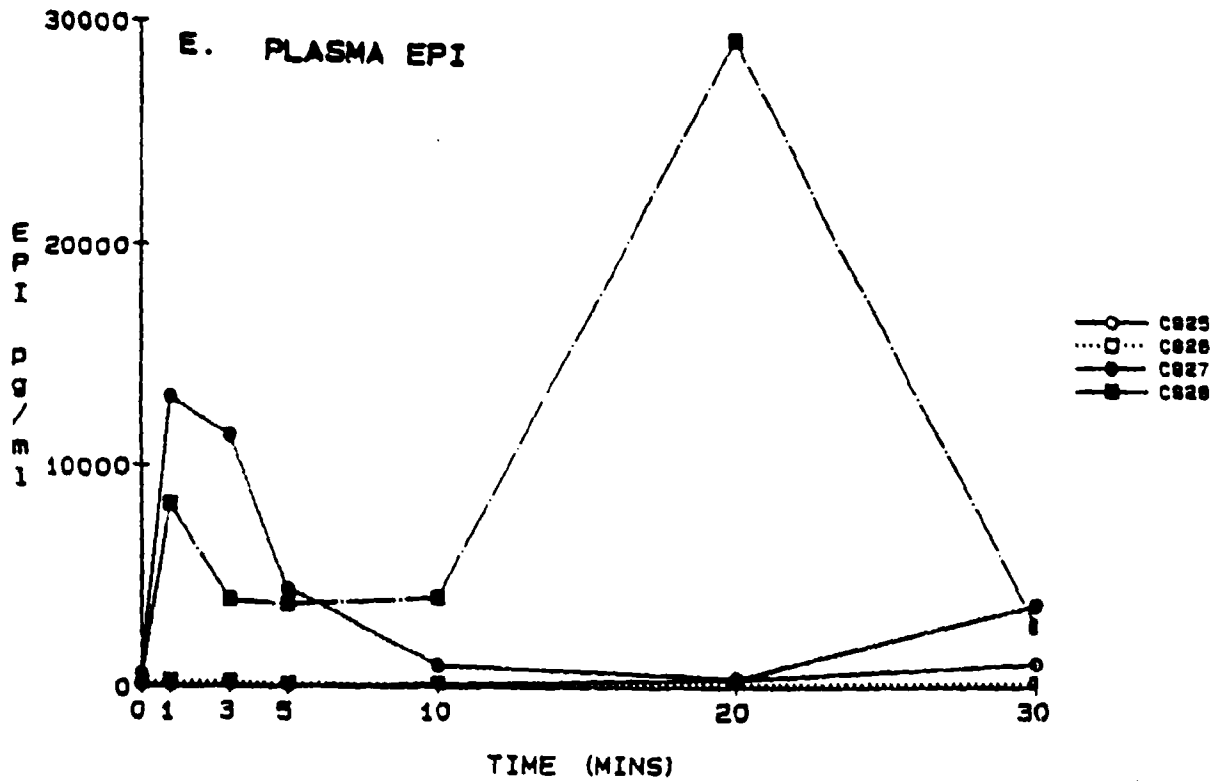

D. PLASMA NE
30000
20000
10000
0
N E p g / m l
0 1 3 5 10 20 30
TIME (MINS)
C025
C026
C027
C028

Fig 14. (cont'd)


E. PLASMA EPI
EPI pg/ml
30000
20000
10000
0
0 1 3 5 10 20 30
TIME (MINS)
C025
C026
C027
C028

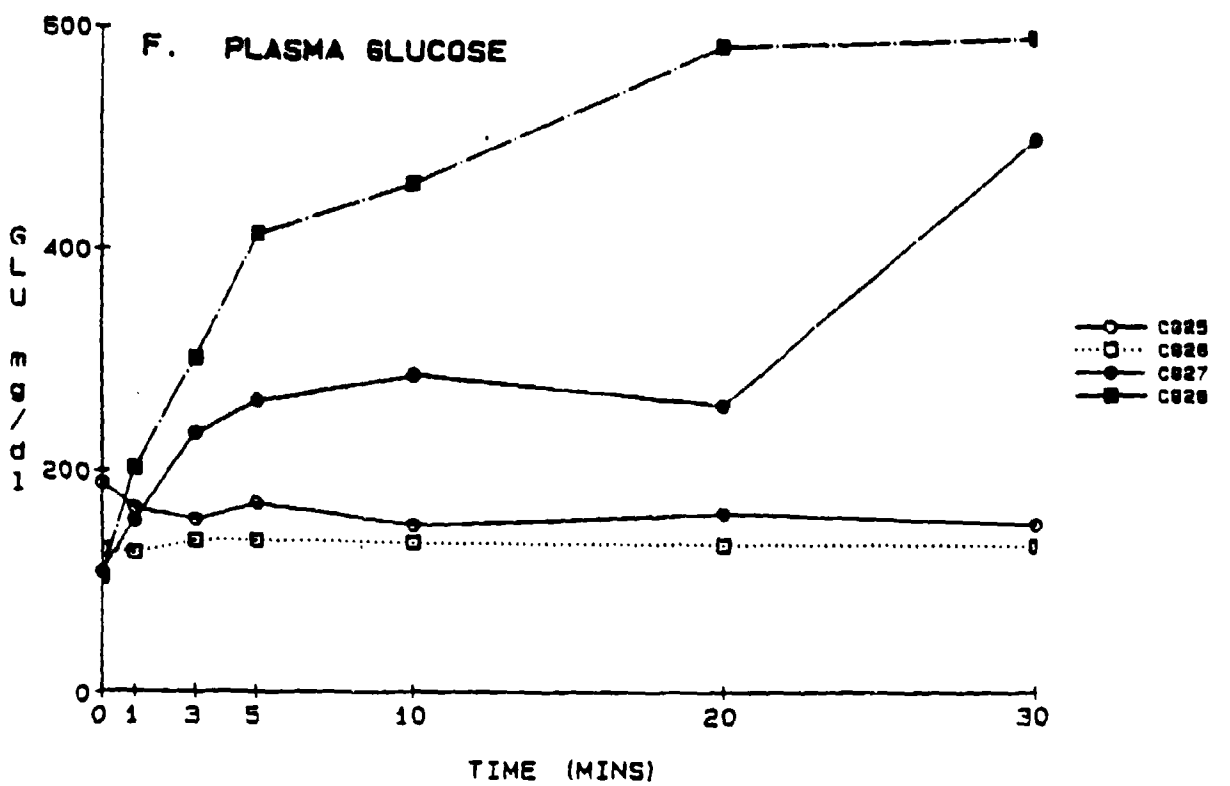

F. PLASMA GLUCOSE
GLU mg/dl
600
400
200
0
0 1 3 5 10 20 30
TIME (MINS)
C025
C026
C027
C028

Table 10. PHYSIOLOGICAL AND BIOCHEMICAL RESULTS WHEN WOUNDED USING A TRANSVERSE TRAJECTORY

	CONT	1 MIN	3 MIN	5 MIN	10 MIN	20 MIN	30 MIN
MABP							
CG25	80	84	75	75	73	71	69
CG26	107	101	103	102	95	90	87
CG27	99	175	147	97	97	80	47
CG28	143	253	167	120	120	143	79
ICP							
CG25	8	38	33	27	21	16	5
CG26	3	73	73	68	61	45	26
CG27	7	153	105	80	90	88	38
CG28	10	152	76	56	40	87	10
CPP							
CG25	72	46	42	48	52	55	64
CG26	104	28	30	34	34	45	61
CG27	92	22	42	17	7	-8	9
CG28	133	101	91	64	80	56	69
NE							
CG25	2199	1876	1784	1832	1864	3508	6158
CG26	2116	2025	2176	1859	2160	1522	2484
CG27	1204	15234	10730	4886	4321	6840	13002
CG28	1977	7624	5476	4594	5377	30018	10353
EPI							
CG25	119	100	100	92	158	400	1055
CG26	186	265	240	170	172	177	184
CG27	565	13047	11323	4455	984	426	3728
CG28	89	8264	3943	3778	4070	29156	2751
GLU							
CG25	188	166	155	170	150	160	151
CG26	128	125	136	136	134	132	132
CG27	108	154	233	262	285	257	498
CG28	103	201	300	412	458	582	589

GENERAL SIGNIFICANCE

1. When using our standard AP trajectory all the energy levels used (0.9J, 1.4J, 2.4J) elicited immediate and significant elevations in plasma CAs. Although the ICPs in all injury groups were significantly elevated, only the 1.4J and 2.4J groups responded with statistically significant post-injury elevations in MABP. It should be noted that although the immediate rise in MABP for the 0.9J group was not statistically significant, it does not preclude its biological significance because it was associated with a statistically significant plasma CA response.

2. When ICP was elevated artifically to 80 torr by a lateral load or to 80 or 150 torr by a cisterna magna mock CSF infusion, an immediate MABP rise was seen in only four out of ten cases. Of these four cases there is only ONE case in which there was also an IMMEDIATE plasma CA rise. In the other six cases there were no physiological or biochemical responses to the ICP elevation.

3 When the trajectory angle was altered from AP to transverse the injury elicited the same type of responding as animals wounded anterior to posterior, except that the apparent force necessary to elicit the immediate responses appears to be higher. Thus, it may be hypothesized that forces on the brainstem may be a primary contributing factor in immediate plasma CA responding.

4. Therefore, based on the findings in the present report it appears that:

A. An increase in ICP alone, without injury, will cause DELAYED (only) elevations in plasma CAs if the ICP is increased enough so as to elicit a rise in MABP. Even in the case where there is an immediate increase in MABP the plasma CA elevations are still delayed.

B. A missile wound to the brain caused IMMEDIATE elevations in plasma CAs, even though the ICP increase may not have been enough to evoke a significant rise in MABP. The time course of the plasma CA elevations suggest that this effect may not be the result of merely an increase in ICP. The origin of the immediate plasma CA elevations may be the result of pressure forces acting on the brainstem (e.g. displacement) as mildly suggested from the results using a transverse trajectory. It is also possible that brain areas involved in the sympathoadrenal response also partake in the response, but if they do, it probably is not caused by merely increasing ICP.

It is also important to note that ballistic literature (Harvey et al, 1946) indicates that with missile transit there is an extremely rapid (msec) large pressure wave that occurs intracranially. We are unable to reliably quantify either its duration or magnitude in our model but we know that it occurs and this extremely rapid pressure fluctuation affects the

C. The immediate plasma CA response observed in missile wounds to the brain appears to be similar to the fluid-percussion model of brain injury (6). In both models there are also immediate elevations in ICP and MABP.

D. Experiments shortly to be performed will indicate whether an alteration of brain CAs occurs widely throughout the brain after wounding and particularly around the missile tract where the BBB is damaged.

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5. Roozekrans NTP, Porsius AJ, van Zwieten PA: Comparison between the pressor response and the rise in plasma catecholamines by acutely elevated intracranial pressure. Arch Int Pharmacodyn 240:143-157, 1979.

6. Rosner MJ, Newsome HH, Becker DP: Mechanical brain injury:the sympathoadrenal response. J Neurosurgery 61:76-86, 1984.

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SECTION C

BEHAVIORAL TESTING OF BRAIN WOUNDED CATS

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BEHAVIORAL TESTING ON INJURED CATS

The following results are the performances of five cats injured at 0.9J and followed for 72 days (thus far) post-injury. Animals were scored every third day post-injury for 30 days, then weekly thereafter. Controls (3) were also tested, however, there were no effect whatsoever at day 3 post-sham treatment, or sooner when testable, so testing was discontinued at day 12 post-sham treatment. The only discernable effect on the controls was a lack of appetite one to three days post-sham treatment, which is presumably because of anesthesia.

On our scoring protocol (see score sheet), items 1-5 are chiefly used to monitor the physical and neurological status of the animals and as indices to initiate appropriate measures when required. These items are very insensitive and are not used in our cumulative scores. Items 6-8 are gross evaluations and, while informative, do not lend themselves to meaningful cumulative scoring either.

The Beam Balance scores (item 9, table 1, fig.1) have proven to be a very powerful indicator of the animals motor system status and abilities. As can be seen, the animals are not generally able to even traverse the beam until approximately 21-24 days post-injury (score="5"), although there is variability from case to case. Even after the animal can walk the beam, the ability to turn right or left on the beam is impaired, but does improve with time. The ability to turn or not in one direction or the other and the quality of the turn was the basis for us modifying the scoring criteria so that we can make use of these finer differences. Therefore, in the future an eleven point scale will be used instead of the present eight point scale. The Beam Balance will be the primary test in future pharmacological testing.

The Grid Beam (item 10) yields information regarding highly accurate placement of all four paws. Two of the five animals were still unable to perform this task at 72 days post-injury. While the other three animals were able to perform the task, they displayed very slow improvement and are still not performing at an " adequate" level. Therefore, the data from this task will not be presented at this time until a larger pool (N) is collected. This task bears closer examination because animals performing well on all aspects of the beam balance do not necessarily perform well on the grid beam. This test may be of great value in the future after further testing.

In Visual Placing (item 11, table 2, fig.2) the animals performed rather poorly until days 21-30 post-injury. It should be noted that the scoring includes a score from each front paw--one affected by the injury, the other unnaffected. Therefore,

unless a normally unaffected paw is affected, the lowest possible score is "5". If the score was lower, the animal would require closer observation and/or exclusion from the experiment due to possible wider ranging problems. The data collected suggest that this test is also very discriminating.

In Non-Visual Placing (item 12, table 3, fig.3) the injured animals also responded very poorly until about 21-36 days post-injury. The non-visual placing ability appears to return, but in a very slow time course. As with the visual placing rationale, the lowest probable score is a "5". Non-visual placing also appears to be a potent discriminator of motor system injury which recovers over a long period of time and will be of great benefit in pharmacological testing.

The Sensorimotor Latency test (item 13) appears to be the least valuable test. Although the test measures the ability to feel different water temperatures and withdraw the paw from the water, this modality seems to be permanently affected (thus far). The injury appears to eliminate 1. the ability to feel 40 C water in ALL animals and 2. the ability to feel 10 C water in most animals (4/5). In no case was the ability to feel 60 C severely impaired nor was there any improvement in latency to withdrawal at other water temperatures. The usability of this test is presently being questioned by us, however, further evaluations in ongoing animals will bear this out.

Therefore it appears that we have at least three excellent behavioral tests: Beam Balance, Visual Placing and Non-Visual Placing. In an effort to provide an overall graph of improvements figure 4 (table 4) displays the cumulative scores of all three of these tests per cat per day. Figure 5 (table 5) displays the same data, except that the two placing scores were averaged before being added to the beam balance score. The rationale for averaging the two placing scores was that both tests are measuring some overlapping modalities, therefore, to prevent placing scores (MAX= 7 and 8) from adversely affecting the beam balance score (MAX=8), the two placing scores were averaged so that the beam balance score would make up at least half the total score. In each case the animals are continually improving for about 30 to 48 days post-injury with the most rapid recovery occuring between 18 to 30 days post-injury.

SIGNIFICANCE

1. The present battery of tests have been found to be much more discriminating than the prior test battery presented in the 1985-1986 report. Under the old test battery wounded cats appeared "recovered" after about 7 days. Using the new test battery there is no substantial recovery for about 30 days or more.

2. THESE RESULTS INDICATE THAT WE HAVE DEVELOPED A RELIABLE TEST BY WHICH DRUGS WHICH IMPROVE NEUROLOGIC FUNCTIONING AFTER MISSILE WOUNDING CAN BE TESTED. DRUG TESTING WILL BEGIN IN THE NEXT SEVERAL MONTHS.

3. AS A COROLLARY OF THE ABOVE, WE MUST HAVE RELIABLE, FRIENDLY CATS SUCH AS CAN NOT BE PROVIDED BY A POUND. WE HAVE BEGUN A KITTEN COLONY WHICH WILL BE EXPENSIVE TO MAINTAIN. USING SUCH CATS WITH OUR PARADIGM ALLOWS THE ONLY REALISTIC TESTING OF DRUGS ON BRAIN-WOUNDED ANIMALS TO SEE WHETHER THEY CAN IMPROVE THE QUALITY OF NEUROLOGIC FUNCTIONING.

CAT #

ITEM #

SAMPLE SCORE SHEET

1. DIET
   Amount given
   Weight left
   Amount consumed
   Score

2. WATER
   Amount given
   Evap volume
   Volume left
   Amount consumed
   Score

3. SENSORY
   Score (1-3)

4. LEVEL OF CONSCIOUSNESS
   Score (1-3)

5. VISION
   Field Cut:
   Score (R2,R1)
   (L2,L1)
   Pupillary:
   Score (R2,R1)
   (L2,L1)

6. AUDITORY
   Orientation (R2,L2)
   NO Orient. (R1,L1)

7. MOTOR FUNCTION
   Score (1-6)
   NB right,left
   fore/hind limb

8. CIRCLING
   Score (Y=1,N=3)

9. BEAM BALANCE
   Score (0-2)

10. GRID BEAM
    Score (# missteps)

11. VISUAL PLACING
    (a) Both (1-3)
    (b) R (1-2)
    (c) L (1-2)

12. NON-VISUAL PLACING
    (a) Right (1-6)
    (b) Left (1-6)

13. SENSORY MOTOR
    Latencies:
    Right fore
    10
    40
    60
    Left fore
    10
    40
    60

COMMENTS:

Fig 1. BEAM BALANCE PERFORMANCE IN WOUNDED (0.9J) CATS

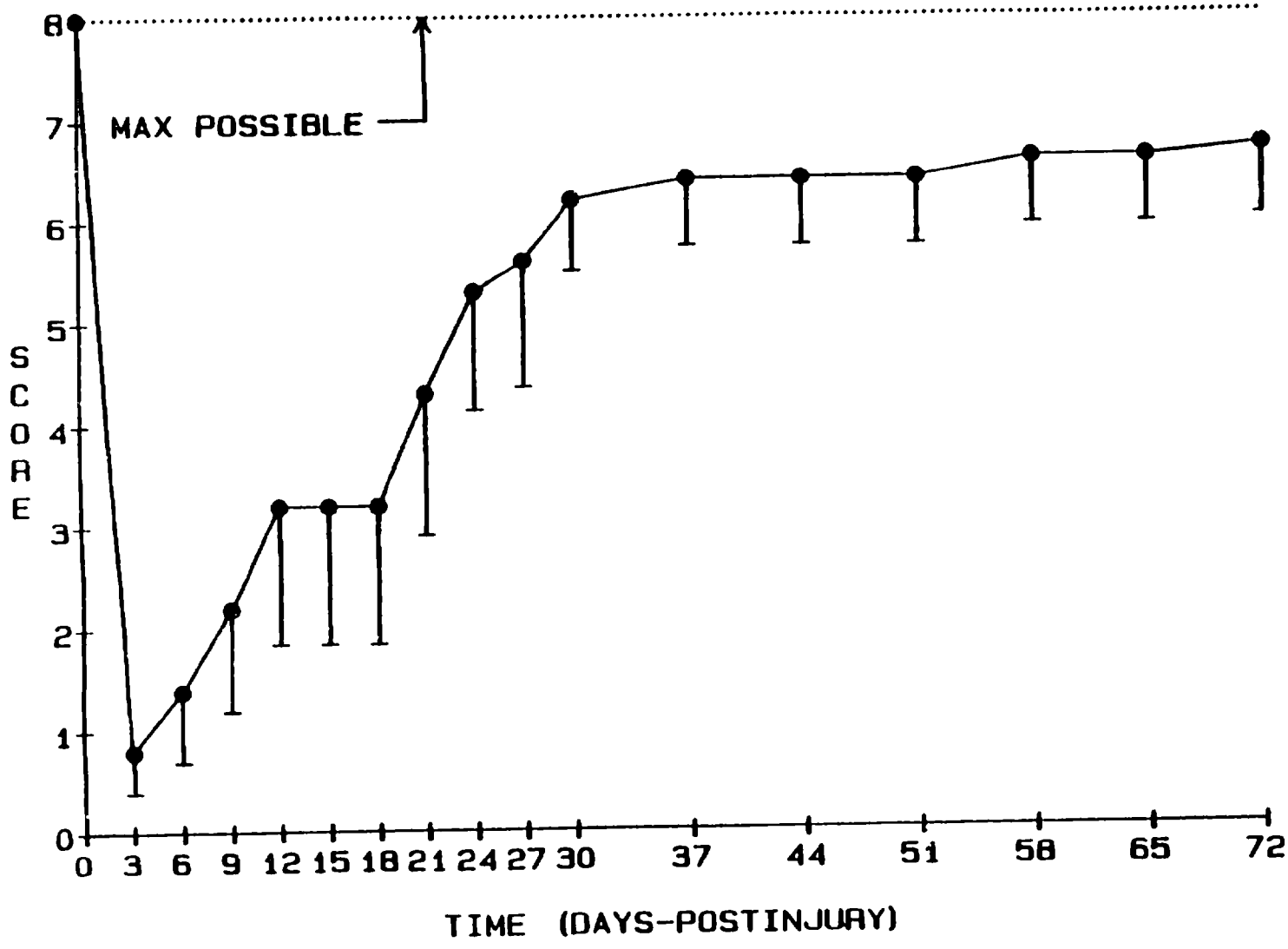

Fig 2. VISUAL PLACING PERFORMANCE IN WOUNDED (0.9J) CATS

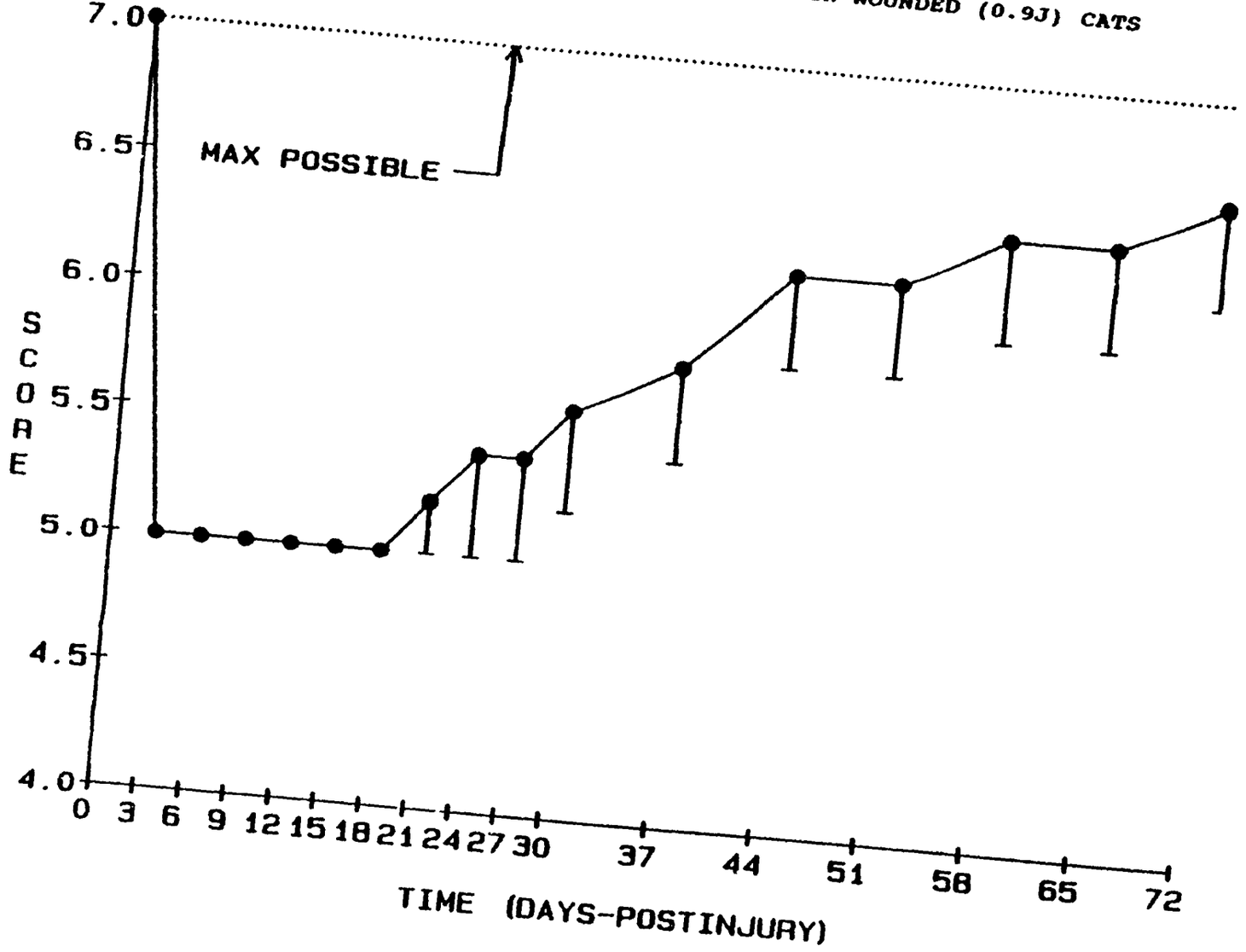

Fig 3. NON-VISUAL PLACING PERFORMANCE IN WOUNDED (0.9J) CATS

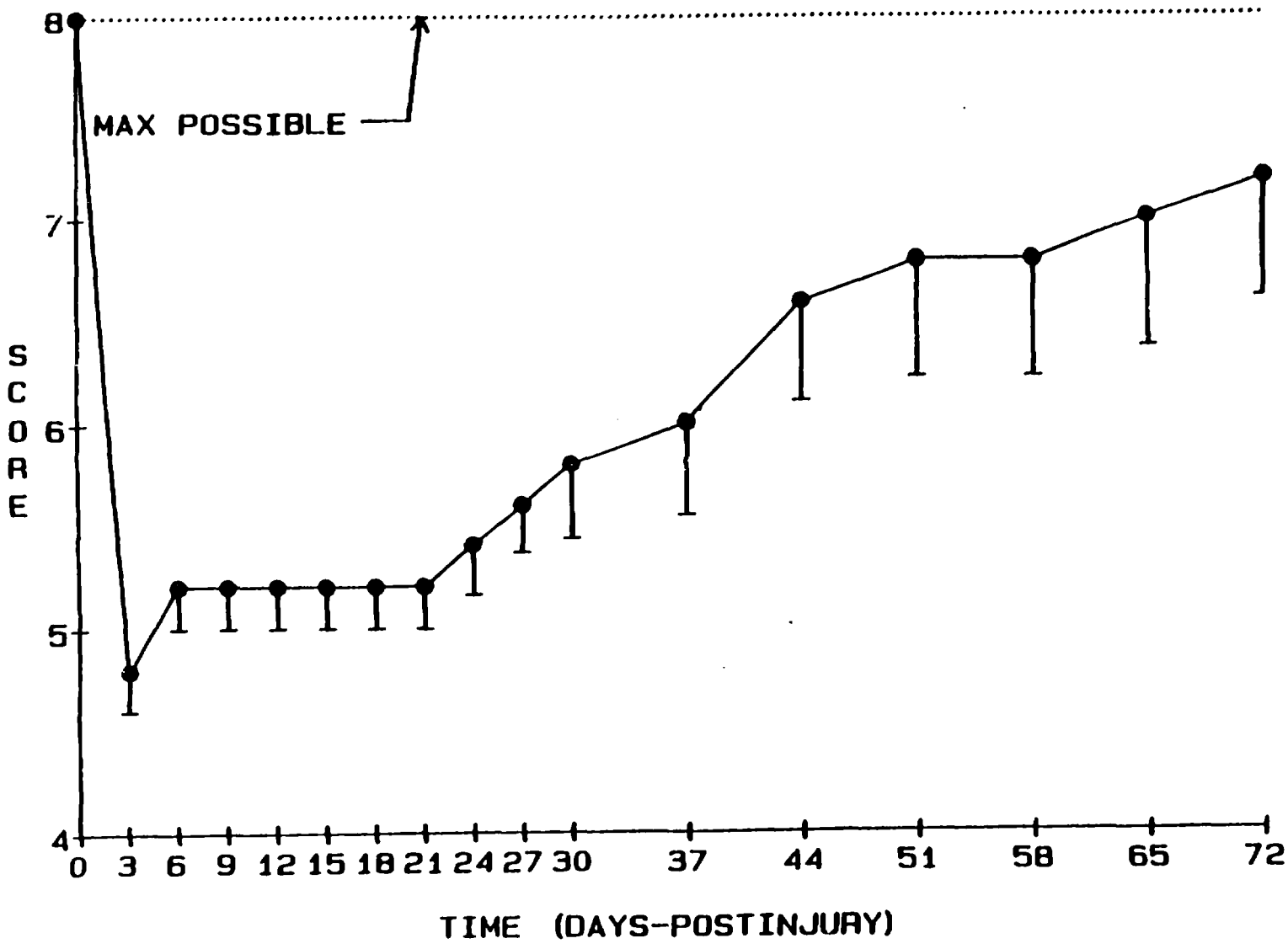

Fig 4. SUM OF THE SCORE RESULTS OF THE BEAM BALANCE AND TWO PLACING TESTS IN WOUNDED (0.9J) CATS

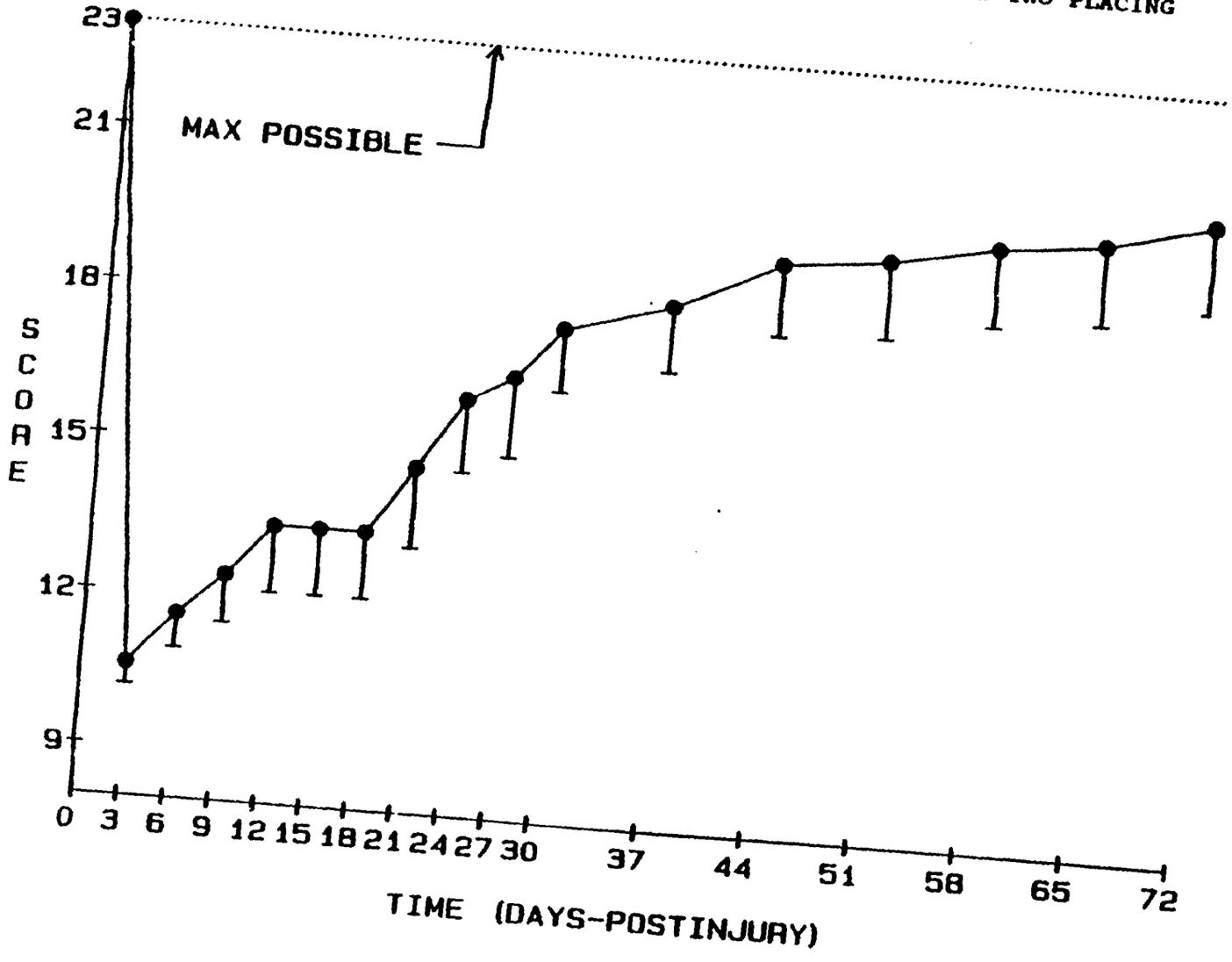

Fig 5. SUM OF THE SCORE RESULTS OF THE BEAM BALANCE PLUS THE AVERAGE OF THE TWO PLACING TESTS IN WOUNDED (0.9J) CATS

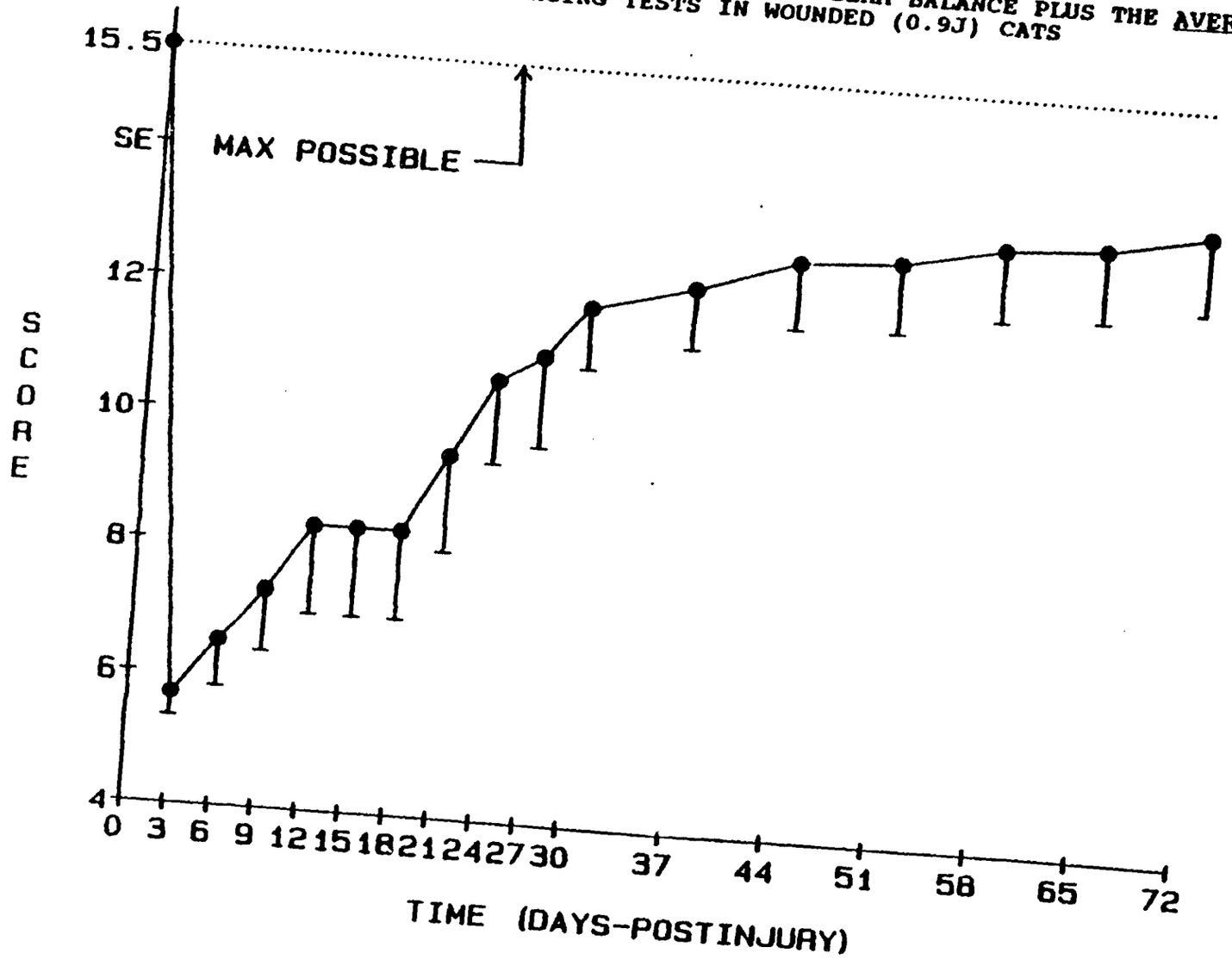

Table 1. BEAM BALANCE PERFORMANCE OF WOUNDED (0.9J) CATS

CAT	CONT	3 days	6 days	9 days	12 days	15 days	18 days	21 days
553	8.00	2.00	4.00	6.00	7.00	7.00	7.00	7.00
745	8.00	0.00	1.00	1.00	1.00	1.00	1.00	5.00
549	8.00	0.00	0.00	2.00	1.00	1.00	1.00	1.00
315	8.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
546	8.00	1.00	1.00	1.00	6.00	6.00	6.00	7.50
MEAN	8.00	0.80	1.40	2.20	3.20	3.20	3.20	4.30
(+/-SEM)	0.00	0.40	0.70	1.00	1.35	1.35	1.35	1.40

CAT	24 days	27 days	30 days	37 days	44 days	51 days	58 days	65 days
553	7.00	7.00	7.00	7.00	7.00	7.00	7.00	7.00
745	5.00	5.00	5.00	6.00	6.00	6.00	7.00	7.00
549	1.00	1.00	4.00	4.00	4.00	4.00	4.00	4.00
315	6.00	7.50	7.50	7.50	7.50	7.50	7.50	7.50
546	7.50	7.50	7.50	7.50	7.50	7.50	7.50	7.50
MEAN	5.30	5.60	6.20	6.40	6.40	6.40	6.60	6.60
(+/-SEM)	1.16	1.24	0.70	0.66	0.66	0.66	0.66	0.66

CAT	72 days
553	7.00
745	7.00
549	4.00
315	7.50
546	8.00
MEAN	6.70
(+/-SEM)	0.70

Table 2. VISUAL PLACING PERFORMANCE OF WOUNDED (0.9J) CATS

CAT	CONT	3 days	6 days	9days	12 days	15 days	18 days	21 days
553	7.00	5.00	5.00	5.00	5.00	5.00	5.00	5.00
745	7.00	5.00	5.00	5.00	5.00	5.00	5.00	5.00
549	7.00	5.00	5.00	5.00	5.00	5.00	5.00	5.00
315	7.00	5.00	5.00	5.00	5.00	5.00	5.00	5.00
546	7.00	5.00	5.00	5.00	5.00	5.00	5.00	6.00
MEAN	7.00	5.00	5.00	5.00	5.00	5.00	5.00	5.20
(+/-SEM)	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.20

CAT	24 days	27 days	30 days	37 days	44 days	51 days	58 days	65 days
553	5.00	5.00	6.00	6.00	7.00	7.00	7.00	7.00
745	5.00	5.00	5.00	6.00	6.00	6.00	6.00	6.00
549	5.00	5.00	5.00	5.00	5.00	5.00	5.00	5.00
315	5.00	5.00	5.00	5.00	6.00	6.00	7.00	7.00
546	7.00	7.00	7.00	7.00	7.00	7.00	7.00	7.00
MEAN	5.40	5.40	5.60	5.80	6.20	6.20	6.40	6.40
(+/-SEM)	0.40	0.40	0.40	0.37	0.37	0.37	0.40	0.40

CAT	72 days
553	7.00
745	7.00
549	5.00
315	7.00
546	7.00
MEAN	6.60
(+/-SEM)	0.40

Table 3. NON-VISUAL PLACING PERFORMANCE OF WOUNDED (0.9J) CATS

CAT	CONT	3 days	6 days	9 days	12 days	15 days	18 days	21 days
553	8.00	5.00	5.00	5.00	5.00	5.00	5.00	5.00
745	8.00	5.00	6.00	6.00	6.00	6.00	6.00	6.00
549	8.00	5.00	5.00	5.00	5.00	5.00	5.00	5.00
315	8.00	4.00	5.00	5.00	5.00	5.00	5.00	5.00
546	8.00	5.00	5.00	5.00	5.00	5.00	5.00	5.00
MEAN	8.00	4.80	5.20	5.20	5.20	5.20	5.20	5.20
(+/-SEM)	0.00	0.20	0.20	0.20	0.20	0.20	0.20	0.20

CAT	24 days	27 days	30 days	37 days	44 days	51 days	58 days	65 days
553	6.00	6.00	7.00	7.00	8.00	8.00	8.00	8.00
745	6.00	6.00	6.00	6.00	7.00	7.00	7.00	8.00
549	5.00	5.00	5.00	5.00	5.00	5.00	5.00	5.00
315	5.00	5.00	5.00	5.00	6.00	6.00	6.00	6.00
546	5.00	6.00	6.00	7.00	7.00	8.00	8.00	8.00
MEAN	5.40	5.60	5.80	6.00	6.60	6.80	6.80	7.00
(+/-SEM)	0.24	0.24	0.37	0.45	0.50	0.58	0.58	0.63

CAT	72 days
553	8.00
745	8.00
549	5.00
315	7.00
546	8.00
MEAN	7.20
(+/-SEM)	0.58

Table 4. SUM OF THE SCORE RESULTS OF THE BEAM BALANCE AND TWO PLACING TESTS IN WOUNDED (0.9J) CATS

CAT	CONT	3 days	6 days	9 days	12 days	15 days	18 days	21 days
553	23.00	12.00	14.00	16.00	17.00	17.00	17.00	17.00
745	23.00	10.00	12.00	12.00	12.00	12.00	12.00	16.00
549	23.00	10.00	10.00	12.00	11.00	11.00	11.00	11.00
315	23.00	10.00	11.00	11.00	11.00	11.00	11.00	11.00
546	23.00	11.00	11.00	11.00	16.00	16.00	16.00	18.50
MEAN	23.00	10.60	11.60	12.40	13.40	13.40	13.40	14.70
(+/-SEM)	0.00	0.40	0.68	0.93	1.29	1.29	1.29	1.56

CAT	24 days	27 days	30 days	37 days	44 days	51 days	58 days	65 days
553	18.00	18.00	20.00	20.00	22.00	22.00	22.00	22.00
745	16.00	16.00	16.00	18.00	19.00	19.00	20.00	21.00
549	11.00	11.00	14.00	14.00	14.00	14.00	14.00	14.00
315	16.00	17.50	17.50	17.50	19.50	19.50	20.50	20.50
546	19.50	20.50	20.50	21.50	21.50	22.50	22.50	22.50
MEAN	16.10	16.60	17.60	18.20	19.20	19.40	19.80	20.00
(+/-SEM)	1.44	1.58	1.22	1.27	1.42	1.51	1.52	1.54

CAT	72 days
553	22.00
745	22.00
549	14.00
315	21.50
546	23.00
MEAN	20.50
(+/-SEM)	1.64

Table 5. SUM OF THE SCORE RESULTS OF THE BEAM BALANCE PLUS THE AVERAGE OF THE TWO PLACING TESTS IN WOUNDED (0.9J) CATS

CAT	CONT	3 days	6 days	9 days	12 days	15 days	18 days	21 days
553	16	7.00	9.00	11.00	12.00	12.00	12.00	12.00
745	16	5.00	6.50	6.50	6.50	6.50	6.50	10.50
549	16	5.00	5.00	7.00	6.00	6.00	6.00	6.00
315	16	5.50	6.00	6.00	6.00	6.00	6.00	6.00
546	16	6.00	6.00	6.00	11.00	11.00	11.00	11.00
MEAN	16	5.70	6.50	7.10	8.10	8.10	8.10	9.50
(+/-SEM)	0.00	0.37	0.67	0.94	1.32	1.32	1.32	1.48

CAT	24 days	27 days	30 days	37 days	44 days	51 days	58 days	65 days
553	12.50	12.50	13.50	13.50	14.50	14.50	14.50	14.50
745	10.50	10.50	10.50	12.00	12.50	12.50	13.50	14.00
549	6.00	6.00	9.00	9.00	9.00	9.00	9.00	9.00
315	11.00	12.50	12.50	12.50	13.50	13.50	14.00	14.00
546	13.50	14.00	14.00	14.50	14.50	15.00	15.00	15.00
MEAN	10.70	11.10	11.90	12.30	12.80	12.90	13.20	13.30
(+/-SEM)	1.39	1.39	0.94	0.93	1.02	1.07	1.08	1.09

CAT	72 days
553	14.50
745	14.50
549	9.00
315	14.50
546	15.50
MEAN	13.60
(+/-SEM)	1.17

APPENDIX

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Table I-A: Changes in physiological parameters in unwounded normotensive (control) cats during 5 consecutive measurements in an experimental period of 100 minutes.
No significant differences observed; Mean +SE.

TIME (min)	CONTROL	5	20	45	90
MABP (mm Hg)	116.01 9.49	120.27 9.27	126.93 10.02	131.36 9.19	142.07 11.83
ICP (mm Hg)	11.29 2.28	10.57 2.19	11.00 2.43	12.43 2.66	12.00 2.59
CPP (mm Hg)	104.73 10.29	109.70 10.40	115.93 11.20	118.93 10.24	130.07 11.66
pH	7.39 0.03	7.35 0.03	7.37 0.03	7.36 0.03	7.34 0.03
PaCO2 (mm Hg)	32.73 0.80	32.07 1.05	31.91 1.42	31.46 0.94	31.16 0.96
PaO2 (mm Hg)	127.00 8.69	127.57 8.72	129.00 8.60	132.86 7.89	135.29 7.96
[H+] (nmol/l)	41.81 3.01	45.17 3.38	43.53 2.87	44.46 2.61	46.26 3.37
BLOOD GLUCOSE (mg/dl)	240.49 19.37	242.86 17.45	235.98 15.51	224.31 19.75	248.59 30.56
HEMATOCRIT (%).	31.50 1.68	31.64 1.67	30.00 1.90	29.57 2.13	30.57 2.88
CVR (CPP/tCBF)	2.91 0.26	2.71 0.34	3.13 0.29	3.62 0.45	3.68 0.30

Table I-B: Changes in rCBF (ml/100g/min) in unwounded normotensive (control) cats during 5 consecutive measurements in an experimental period of 100 minutes.
L = Left hemisphere; R = Right hemisphere
No significant differences observed; Mean +SE.

TIME (min)	CONTROL	5	20	45	90
CAUDATE L+R	56.71 9.00	62.57 13.37	56.43 8.58	58.57 11.50	58.71 7.62
HIPPOCAMPUS L	21.43 2.92	26.00 4.13	23.86 2.94	22.14 2.35	21.00 2.94
HIPPOCAMPUS R	24.57 2.86	27.86 4.16	25.43 2.51	25.57 3.21	24.14 2.60
THALAMUS L	43.29 7.66	54.86 11.06	45.43 4.91	44.29 6.80	48.14 5.92
THALAMUS R	42.43 6.59	60.00 17.19	46.86 4.51	42.86 5.91	44.29 4.56
SEPTUM & HYPOTHALAMUS	19.14 3.38	22.71 5.04	21.57 2.95	19.14 3.00	20.29 3.15
RETICULAR FORMATION	47.57 11.50	54.86 13.52	44.71 5.98	41.57 6.76	43.14 6.73
MIDBRAIN	37.71 9.40	41.86 10.01	34.00 3.73	31.43 3.58	34.86 4.36
PONS	19.43 8.62	19.00 5.40	15.86 2.56	14.00 1.80	14.86 3.73
MEDULLA	40.71 8.84	44.00 6.67	38.00 3.49	32.29 1.73	31.29 3.52
CEREBELLUM-GRAY L	43.29 3.06	54.86 8.69	46.14 4.82	44.29 6.73	39.29 5.51
CEREBELLUM-GRAY R	45.43 6.14	50.29 7.41	43.29 3.71	40.86 4.13	38.86 5.09
CEREBELLUM-WHITE	48.43 5.35	52.14 7.51	49.14 6.96	40.86 4.85	36.71 4.91

(Continued)

Table I-B continued

TIME (min)	CONTROL	5	20	45	90
FRONTAL CORTEX L	38.43	47.71	42.86	40.71	43.57
	3.06	10.09	5.97	6.01	4.53
PARIETAL CORTEX L	42.00	53.57	41.57	40.14	44.86
	5.90	13.06	5.58	7.32	3.92
TEMPORAL CORTEX L	28.43	37.29	31.43	28.71	31.71
	2.63	6.74	4.37	4.21	4.13
OCCIPITAL CORTEX L	45.50	54.17	41.67	37.17	45.50
	6.24	12.61	4.46	3.37	2.62
FRONTAL CORTEX R	38.00	47.86	40.43	39.00	41.43
	3.36	8.68	4.76	4.80	3.15
PARIETAL CORTEX R	41.00	48.86	45.29	38.29	43.14
	7.27	13.62	6.78	5.99	5.57
TEMPORAL CORTEX R	29.29	37.14	33.71	29.00	29.29
	3.41	8.89	5.44	5.51	3.56
OCCIPITAL CORTEX R	42.00	50.00	48.67	41.83	50.17
	4.02	6.93	5.52	3.55	3.22
WHITE MATTER L	32.00	37.43	31.57	28.71	30.29
	2.84	5.34	2.51	3.43	2.39
WHITE MATTER R	34.43	37.57	33.57	30.57	32.00
	3.14	4.77	2.36	2.72	3.85
WHOLE BRAIN	37.24	45.07	38.07	35.00	36.20
	3.91	7.55	3.68	4.54	3.40

Table I-C: Changes in organ blood flows in unwounded normotensive (control) cats during 5 consecutive measurements in an experimental period of 100 minutes.
* Significant as compared to control; $p<0.05$; Mean +SE.

TIME (min)	CONTROL	5.00	20.00	45.00	90.00
CARDIAC MUSCLE	259.14 49.19	266.71 63.38	253.86 56.59	251.29 59.53	276.43 71.52
ADRENALS	657.86 94.69	542.00 71.49	489.57 68.15	419.71 41.23	407.00 52.39
SPLEEN	128.20 29.94	134.60 31.38	117.60 31.71	135.40 49.18	124.20 35.59
KIDNEY-CORTEX	261.00 24.82	280.00 16.22	227.71 28.69	218.14 28.69	190.43 26.10
KIDNEY-MEDULLA	30.64 10.88	27.99 11.38	23.57 10.14	24.66 9.28	22.09 8.68
SKELETAL MUSCLE	4.06 1.23	4.19 0.78	2.77 0.30	2.79 0.30	3.07 0.46
SPINAL CORD	18.29 4.53	20.43 4.21	15.57 2.16	14.14 1.82	16.57 3.58
BRONCHIAL FLOW/ TOTAL PERIPHERAL SHUNTING	38.33 12.43	36.83 14.17	33.00 9.41	20.33 6.24	10.33* 5.28

Table II-A: Changes physiological parameters in wounded normotensive cats before (control), and at 5, 20, 45 and 90 min after BMW. * Significant as compared to control; $p<0.05$; Mean +SE.

TIME (min)	CONTROL	5	20	45	90
MABP (mm Hg)	133.63 12.41	123.37 16.49	116.00 15.88	114.37 20.90	127.76 28.06
ICP (mm Hg)	8.71 1.91	63.57* 11.89	46.19* 7.23	41.64* 5.35	43.80* 8.91
CPP (mm Hg)	124.91 12.15	59.80 22.12	69.81 20.17	72.73 20.72	83.96 20.02
pH	7.38 0.02	7.34 0.03	7.31 0.05	7.28 0.06	7.29 0.05
PaCO2 (mm Hg)	32.33 1.00	30.51 0.99	31.30 1.23	29.16 1.86	31.90 3.33
PaO2 (mm Hg)	127.33 6.89	128.67 7.52	124.67 5.73	126.00 4.16	133.00 5.45
[H+] (nmol/l)	42.19 1.79	46.14 3.68	51.14 3.46	54.79 8.23	52.44 7.16
BLOOD GLUCOSE (mg/dl)	185.02 20.69	242.72 44.80	270.88 60.37	319.02 64.13	258.63 57.78
HEMATOCRIT (%)	31.71 2.49	31.27 2.36	30.33 2.19	28.83 2.17	30.60 3.31
CVR (CPP/tCBF)	3.53 0.47	2.26 0.65	2.43 0.63	2.69 0.64	3.32 0.92

Table II-B: Changes in rCBF (ml/100g/min) in wounded normotensive cats before (control) and at 5, 20, 45 and 90 min after BMW.
L = Left hemisphere; R = Right hemisphere
* Significant as compared to control; $p<0.05$; Mean ±SE.

TIME (min)	CONTROL	5	20	45	90
FRONTAL CORTEX L	37.29 3.15	32.86 5.39	28.14 2.44	26.29 1.84	24.20* 2.33
PARIETAL CORTEX L	38.43 2.43	34.00 5.47	30.57 3.93	29.00 2.98	28.00 3.63
TEMPORAL CORTEX L	32.57 4.99	27.57 4.76	24.57 2.79	23.43 2.89	23.40 3.20
OCCIPITAL CORTEX L	58.71 11.77	40.57 11.13	36.71 7.26	34.29 7.39	36.80 6.04
FRONTAL CORTEX R	38.29 5.09	32.86 5.56	27.43 2.33	25.57 2.36	22.80* 3.06
PARIETAL CORTEX R	46.29 6.75	34.71 6.44	29.14* 4.38	32.00 6.31	24.80* 5.96
TEMPORAL CORTEX R	34.14 4.17	24.14 4.64	22.57 2.85	19.71* 1.80	18.60* 1.66
OCCIPITAL CORTEX R	61.86 9.00	34.86* 5.67	35.29* 3.41	38.00* 6.11	27.80* 3.71
WHITE MATTER L	32.86 2.56	26.00 3.64	26.14 2.01	23.71* 1.71	21.60* 2.06
WHITE MATTER R	32.71 4.14	27.29 4.34	24.43 2.69	24.14 2.42	21.00* 3.16
PERIWOUND-GRAY	33.57 3.37	34.29 5.31	33.71 3.94	24.71 2.77	21.80* 3.54
PERIWOUND-WHITE	32.67 3.64	36.57 6.20	37.14 4.34	31.29 3.82	23.20 4.21
WHOLE BRAIN	36.67 2.58	30.14 4.43	29.00 2.13	25.99* 1.20	23.46* 1.92

(Continued)

Table II-8 continued

TIME (min)	CONTROL	5	20	45	90
CAUDATE L+R	47.29 3.97	38.14 9.12	30.71 3.87	32.57 3.40	32.60 4.47
HIPPOCAMPUS L	20.86 2.04	25.71 6.99	19.86 1.03	18.50 1.48	17.20 1.77
HIPPOCAMPUS R	20.17 1.68	24.14 4.31	21.71 2.60	20.71 1.32	17.40 0.68
THALAMUS L	38.86 5.37	41.29 10.58	34.29 5.35	31.29 3.89	32.00 5.34
THALAMUS R	38.71 4.56	36.00 7.69	36.43 7.49	29.14 2.45	26.60 3.47
SEPTUM & HYPOTHALAMUS	19.50 1.96	18.00 4.17	18.14 2.32	16.00 1.29	15.00 1.76
RETICULAR FORMATION	40.29 3.77	33.43 4.42	41.86 8.88	33.29 1.71	33.20 3.64
MIDBRAIN	28.14 2.91	29.71 5.31	31.14 4.75	23.86 2.22	23.00 4.38
PONS	17.17 2.18	14.57 2.64	14.86 1.78	13.57 1.43	13.40 2.71
MEDULLA	38.00 5.83	29.00 5.53	32.14 2.32	24.43 1.74	26.00 5.28
CEREBELLUM-GRAY L	45.43 4.51	37.14 7.44	39.00 3.35	33.29 2.70	34.60 6.07
CEREBELLUM-GRAY R	51.57 5.55	40.43 7.16	42.57 3.93	37.86 4.75	33.60 5.18
CEREBELLUM-WHITE	44.57 4.67	37.71 5.80	40.14 3.40	33.43 3.10	30.00 3.52

Table II-C: Changes in organ blood flows in wounded normotensive cats before and 5, 20, 45 and 90 min after wounding.
* Significant as compared to control; $p<0.05$; Mean ±SE.

TIME (min)	CONTROL	5.00	20.00	45.00	90.00
CARDIAC MUSCLE	254.86 33.00	413.43 145.68	270.86 31.02	239.00 36.25	234.20 46.18
ADRENALS	540.00 70.92	511.86 107.96	408.71 98.52	326.57 70.76	385.60 106.77
SPLEEN	88.60 35.26	47.80 16.11	43.00 14.40	54.80 33.12	81.00 31.50
KIDNEY-CORTEX	303.86 68.91	237.86 69.59	162.71 53.06	163.57 49.56	161.60 58.44
KIDNEY-MEDULLA	38.71 11.49	34.29 11.54	21.00 7.35	18.71 8.07	21.60 10.07
SKELETAL MUSCLE	3.44 0.64	1.87 0.73	2.29 0.71	1.83 0.48	1.64 0.57
SPINAL CORD	15.71 2.12	13.71 2.90	14.71 2.42	12.17 0.31	11.80 2.44
BRONCHIAL FLOW/ TOTAL PERIPHERAL SHUNTING	33.71 9.29	37.71 10.94	30.00 10.30	16.43 4.99	12.80 5.39

Table III-A: Changes in physiological parameters in unwounded hypotensive cats before bleeding (control), at 3 levels of hemorrhagic hypotension (5, 20, 45 min) and after reinfusion (90 min).
* Significant as compared to control: $p<0.05$; Mean ±SE.

TIME (min)	CONTROL	5	20	45	90
MABP (mm Hg)	116.29 5.05	89.29* 5.31	67.61* 3.98	47.83* 5.13	122.05 4.74
ICP (mm Hg)	5.75 1.37	4.50 1.07	4.50 1.18	3.50 1.56	7.50 1.73
CPP (mm Hg)	110.54 5.34	84.79* 6.22	63.11* 4.81	44.32* 5.44	114.55 5.65
pH	7.39 0.02	7.40 0.03	7.30 0.04	7.21* 0.05	7.25* 0.03
PaCO2 (mm Hg)	31.09 1.50	27.72 1.69	27.54 1.30	27.51 2.07	33.43 0.99
PaO2 (mm Hg)	124.71 8.24	130.29 7.12	125.29 8.70	128.33 4.42	125.00 6.55
[H+] (nmol/l)	41.39 1.74	40.44 2.83	51.10 3.66	63.14* 7.62	57.15 4.33
BLOOD GLUCOSE (mg/dl)	204.13 35.75	254.94 49.96	332.60* 65.26	501.40* 45.32	356.53* 45.91
HEMATOCRIT (%)	31.38 3.18	29.64 3.37	28.50 3.35	26.29 2.92	27.17 3.11
CVR (CPP/tCBF)	3.61 0.85	2.91 3.50	2.14 0.43	1.61* 0.23	3.18 0.53

Table III-8: Changes in rCBF (ml/100g/min) in unwounded hypotensive cats before bleeding (control), at 3 levels of hemorrhagic hypotension (5, 20, 45 min) and after reinfusion (90 min). * Significant as compared to control; $p<0.05$; Mean +SE.

TIME (min)	CONTROL	5	20	45	90
FRONTAL CORTEX L	54.16 11.85	42.27 8.88	39.08 6.78	32.89 4.47	42.83 6.01
PARIETAL CORTEX L	54.94 12.19	40.50 6.89	42.27 7.14	33.85 5.36	48.83 9.80
TEMPORAL CORTEX L	38.92 7.83	32.99 6.14	32.40 5.04	28.39 3.07	34.50 5.86
OCCIPITAL CORTEX L	62.76 14.10	49.64 9.43	46.89 8.77	37.10 5.68	55.67 15.01
FRONTAL CORTEX R	42.81 7.46	34.47 4.13	34.33 4.80	32.94 4.85	47.67 8.83
PARIETAL CORTEX R	44.49 8.70	38.33 8.07	35.40 5.80	31.14 4.61	46.67 6.82
TEMPORAL CORTEX R	26.80 4.16	24.87 2.99	26.28 3.34	26.48 3.24	27.50 5.86
OCCIPITAL CORTEX R	47.40 7.69	35.95 4.43	38.91 5.87	33.16 5.56	50.83 9.26
WHITE MATTER L	34.66 5.33	28.86 4.18	31.23 5.21	27.82 4.69	34.33 7.52
WHITE MATTER R	31.60 5.06	28.69 4.17	30.39 4.95	28.29 4.96	34.00 6.92
WHOLE BRAIN	39.01 6.44	33.60 4.46	35.19 5.28	31.27 3.08	42.50 8.90

(Continued)

Table III-B continued

TIME (min)	CONTROL	5	20	45	90
CAUDATE L+R	52.25 4.71	43.52 3.52	46.54 5.40	42.10 6.15	62.17 6.06
HIPPOCAMPUS L	24.03 2.52	25.69 3.41	25.28 3.12	24.63 2.94	28.33 3.67
HIPPOCAMPUS R	22.60 3.05	22.09 2.45	24.38 2.60	25.00 3.69	26.67 3.56
THALAMUS L	39.66 5.48	36.97 3.83	41.60 4.54	39.95 5.46	50.00 10.57
THALAMUS R	42.64 4.87	39.24 4.18	44.12 5.14	39.63 6.01	52.00 8.49
SEPTUM / HYPOTHALAMUS	23.35 2.31	21.46 1.37	22.31 1.39	22.84 2.88	23.67 2.12
RETICULAR FORMATION	39.29 4.99	39.35 5.03	44.67 7.28	41.75 6.48	52.43 10.35
MIDBRAIN	31.44 4.31	28.95 2.90	35.16 3.83	33.59 4.81	35.50 7.57
PONS	15.86 2.71	15.87 2.58	20.74 5.15	19.29 3.73	33.17 14.16
MEDULLA	32.35 4.87	34.35 6.58	36.70 6.51	32.95 7.16	52.86 21.32
CEREBELLUM-GRAY L	41.49 8.43	47.15 13.55	40.95 8.05	34.84 8.81	51.33 14.55
CEREBELLUM-GRAY R	41.60 8.61	44.56 11.58	38.15 6.88	34.89 8.36	48.33 13.11
CEREBELLUM-WHITE	37.84 5.69	41.37 8.77	38.90 6.67	34.02 7.37	47.83 7.94

Table III-C: Changes in organ blood flows in unwounded hypotensive cats before bleeding (control), at 3 levels of hemorrhagic hypotension (5, 20, 45 min) and after reinfusion (90 min). * Significant as compared to control: $p<0.05$; Mean +SE.

TIME (min)	CONTROL	5.00	20.00	45.00	90.00
CARDIAC MUSCLE	258.55 40.01	178.99 24.90	238.55 45.77	239.29 48.30	326.83 53.76
ADRENALS	629.06 130.62	536.52 98.02	453.66 98.06	334.48 66.28	581.50 68.97
SPLEEN	80.67 14.84	9.17* 1.97	17.50* 5.08	20.00* 3.58	64.20 16.40
KIDNEY-CORTEX	254.84 31.91	213.89 31.84	144.88 33.91	79.65* 22.65	240.67 57.97
KIDNEY-MEDULLA	28.81 7.07	27.78 6.54	13.15 5.37	13.74* 3.58	33.17 3.11
SKELETAL MUSCLE	3.00 0.73	2.03 0.56	2.37 0.39	1.50 0.46	3.33 0.88
SPINAL CORD	14.27 2.80	14.41 2.53	16.30 3.71	14.29 2.36	18.67 6.11
BRONCHIAL FLOW/ TOTAL PERIPHERAL SHUNTING	46.50 14.70	22.37 7.28	18.62 7.08	7.50* 4.49	34.50 12.40

Table IV-A: Changes in physiological parameters in wounded hypotensive cats before wounding/bleeding (contol), at 3 levels of hemorrhagic hypotension after wounding (5, 20, 45 min) and following reinfusion (90 min).
* Significant as compared to control; $p<0.05$; Mean +SE.

TIME (min)	CONTROL	5.00	20.00	45.00	90.00
MABP (mmHg)	126.75	105.83	62.95*	43.59*	87.32*
	7.78	10.32	4.56	6.29	9.99
ICP (mmHg)	6.40	59.70*	40.05*	31.10*	60.05*
	1.86	7.16	6.85	8.19	8.11
CPP (mmHg)	120.35	46.13*	22.90*	12.49*	27.27*
	7.35	9.71	6.47	6.41	10.74
C/R	3.23	2.19	1.27	1.68	6.71
	0.53	0.51	0.50	1.83	3.28
pH	7.37	7.33	7.29	7.26	7.26
	0.02	0.03	0.04	0.06	0.04
PaCO2 (mmHg)	32.36	29.87	28.57	24.28*	29.33
	1.09	1.95	1.55	1.52	1.00
PaO2 (mmHg)	121.53	122.72	126.67	122.36	124.57
	7.46	9.46	7.59	8.22	4.90
[H+] n mol/l	42.79	49.41	53.76	61.40	59.10
	1.77	3.91	5.98	12.30	7.20
BLOOD GLUCOSE (mg/dl)	211.01	402.66*	439.63*	389.47*	450.08*
	44.44	75.60	85.87	102.71	50.90
HEMATOCRIT (%)	33.18	30.20	27.67	24.00*	29.30
	3.49	4.12	3.37	1.68	2.62

Table IV-8: Changes in rCBF (ml/100g/min) in wounded hypotensive cats before wounding/bleeding (control), at 3 levels of hemorrhagic hypotension after wounding (5, 20, 45 min) and following reinfusion (90 min).
* Significant as compared to control; $p<0.05$; Mean +SE.

TIME (min)	CONTROL	5	20	45	90
FRONTAL CORTEX L	44.50 6.70	24.20* 4.40	21.40* 5.20	18.50* 6.70	9.70* 3.90
PARIETAL CORTEX L	49.90 7.50	23.80* 5.10	20.10* 6.00	16.40* 6.30	8.70* 3.50
OCCIPITAL CORTEX L	63.00 10.20	23.00* 4.90	19.80* 5.20	15.90* 6.40	9.40* 4.20
TEMPORAL CORTEX L	35.50 7.10	19.80* 3.10	18.10* 4.10	16.10* 4.90	7.50* 2.20
FRONTAL CORTEX R	43.40 6.10	28.00* 6.20	23.10* 5.50	17.40* 7.10	11.50* 6.10
PARIETAL CORTEX R	44.70 7.80	21.80* 4.50	20.20* 5.90	17.20* 6.80	5.70* 2.40
OCCIPITAL CORTEX R	63.40 14.30	27.20* 7.20	21.00* 6.50	16.60* 7.60	13.70* 10.40
TEMPORAL CORTEX R	33.40 4.60	19.30* 3.20	17.90* 4.20	17.20* 6.60	8.50* 3.60
WHITE MATTER L	36.30 3.10	18.50* 3.60	17.10* 4.20	13.30* 4.60	8.20* 3.20
WHITE MATTER R	33.00 3.70	19.40* 4.00	17.10* 4.30	13.30* 4.40	7.10* 3.50
PERIWOUND-GRAY	41.90 5.90	33.80 9.10	26.30* 8.50	15.20* 6.40	6.60* 3.10
PERIWOUND-WHITE	35.50 4.00	30.70 9.60	24.60 8.20	14.00 5.80	9.20* 5.20
WHOLE BRAIN	39.30 4.00	22.30* 3.60	20.60* 4.70	17.00* 5.20	12.20* 4.40

(Continued)

Table IV-8 continued

TIME (min)	CONTROL	5	20	45	90
CAUDATE R+L	62.70 14.30	28.30* 4.30	26.80* 5.20	28.60* 8.40	11.50* 5.20
HIPPOCAMPUS L	23.20 1.90	17.50 3.00	17.00 4.20	14.20 5.40	7.60* 3.00
HIPPOCAMPUS R	21.50 2.30	17.20 3.40	15.50 4.20	13.10 4.70	5.80* 2.30
THALAMUS L	39.90 5.80	23.10 4.30	25.60 7.10	20.70 7.90	11.30* 4.30
THALAMUS R	45.30 6.10	26.10 4.50	25.00 7.10	19.00* 6.80	17.80* 10.30
SEPTUM & HYPOTHALAMUS	23.80 3.30	13.40 2.60	15.90 4.80	13.30 4.90	6.80* 2.70
RETICULAR FORMATION	42.20 2.90	24.50 5.20	23.70 6.60	20.80 7.30	16.10* 7.80
MIDBRAIN	31.10 3.00	27.50 5.00	21.90 4.60	16.50 4.60	12.50* 4.70
PONS	13.80 1.60	12.70 2.40	13.50 3.70	11.80 3.10	8.10 1.80
MEDULLA	37.10 3.50	21.30* 3.50	22.00* 4.20	19.80* 5.40	14.30* 3.60
CEREBELLUM-GRAY L	48.80 7.00	26.20* 4.10	23.40* 4.10	18.50* 5.60	22.70* 9.00
CEREBELLUM-GRAY R	41.40 5.70	27.00 3.90	24.70 4.20	19.00* 5.40	21.50* 9.20
CEREBELLUM-WHITE	39.70 5.40	24.20 3.50	24.10 3.90	20.10* 4.60	20.10* 6.90

Table IV-C: Changes in organ blood flows in wounded hypotensive cats before wounding/bleeding (control), at 3 levels of hemorrhagic hypotension after wounding (5, 20, 45 min) and following reinfusion (90 min).
* significant as compared to control; $p<0.05$; Mean +SE.

TIME (min)	CONTROL	5.00	20.00	45.00	90.00
CARDIAC MUSCLE	242.10 23.05	293.30 49.70	217.30 28.20	191.80 21.58	198.90 24.61
ADRENALS	179.80 72.00	411.00 68.41	285.70 38.72	176.40* 33.33	372.00 81.71
SPLEEN	108.00 24.37	55.29* 9.24	50.86* 15.86	39.71* 15.05	65.29 13.38
KIDNEY-CORTEX	321.50 57.09	236.00 62.15	183.90 33.21	80.50* 19.95	220.60 41.81
KIDNEY-MEDULLA	39.52 3.99	31.67 8.45	30.13 9.83	14.35 3.14	33.99 13.58
SKELETAL MUSCLE	3.27 0.58	1.32 0.47	2.30 0.85	1.80 0.85	1.90 0.59
SPINAL CORD	18.70 3.07	17.10 2.85	15.40 2.97	16.08 3.41	15.05 2.54
BRONCHIAL FLOW/ TOTAL PERIPHERAL SHUNTING	50.60 13.79	24.70 5.11	14.40* 3.84	5.90* 1.16	28.00 8.01

Table V-A: Changes in physiological parameters in response to hypercapnia before and after BMW.
* significant as compared to pre- and post-wounding normocapnia respectively; $p<0.05$; Mean +SE.

	BEFORE WOUNDING		AFTER WOUNDING	
	NORMOCAPNIA	HYPERCAPNIA	NORMOCAPNIA	HYPERCAPNIA
MABP (mm Hg)	137.20 24.32	148.00 29.38	110.60 13.17	107.60 9.05
ICP (mm Hg)	9.80 3.81	12.00 3.36	39.00 11.09	34.00 5.81
CPP (mm Hg)	127.40 22.01	136.00 27.14	71.60 9.67	73.80 10.80
CVR	3.77 0.51	1.95 0.46	3.11 0.59	3.59 0.84
pH	7.41 0.03	7.17* 0.02	7.29 0.05	7.08* 0.06
PaCO2 (mm Hg)	29.46 1.73	53.60* 2.51	31.54 2.43	56.08* 3.24
PaO2 (mm Hg)	130.80 6.83	128.60 9.25	124.20 9.99	125.80 9.28
[H+] n mol/l	38.90	67.60*	51.30	83.20*
BLOOD GLUCOSE (mg/dl)	213.52 39.27	261.70 62.06	398.44 77.76	391.50 78.54
HEMATOCRIT (%)	27.90 2.66	30.00 2.85	29.40 1.08	30.20 1.93

Table V-8: Changes in rCBF (ml/100g/min) in reponse to hypercapnia before and after BMW.
* Significant as compared to pre- and post-wounding normocapnia respectively; $p<0.05$; Mean +SE.

	BEFORE WOUNDING		AFTER WOUNDING	
	NORMOCAPNIA	HYPERCAPNIA	NORMOCAPNIA	HYPERCAPNIA
FRONTAL CORTEX	41.20 6.63	97.80* 5.41	22.80 4.14	25.60 7.76
PARIETAL CORTEX	38.00 6.03	81.80* 3.51	19.60 2.58	21.60 5.10
TEMPORAL CORTEX	27.40 4.39	64.80* 4.73	27.40 7.70	21.80 5.80
OCCIPITAL CORTEX	43.20 5.88	91.20* 5.83	24.80 3.64	25.60 6.35
WHITE MATTER	30.80 2.22	81.60* 3.84	20.20 3.51	24.80 6.13
CAUDATE NUCLEUS	44.20 4.78	115.80* 19.05	26.60 2.46	36.40 8.79
HIPPOCAMPUS	25.40 5.15	49.00* 5.68	21.00 4.69	20.40 4.56
THALAMUS	35.40 4.35	75.20* 4.97	24.60 2.20	33.60 7.41
HYPOTHALAMUS	20.80 3.34	58.00* 7.16	19.80 5.44	19.00 4.95
RETICULAR FORMATION	34.40 2.79	82.20* 4.21	28.60 3.85	34.80 7.21
BRAINSTEM & MEDULLA	29.40 3.31	60.20* 4.21	28.20 5.56	24.40 5.78
CEREBELLUM-GRAY	39.60 7.38	78.40* 5.67	37.60 13.75	30.80 9.89
CEREBELLUM-WHITE	42.20 4.03	74.40* 6.21	31.80 5.93	31.00 7.04
PERIWOUND-GRAY	34.00 2.88	69.20* 1.88	46.00 14.30	27.00 6.40
PERIWOUND-WHITE	30.60 3.08	63.60* 3.66	50.40 14.55	30.20 8.52
WHOLE BRAIN	33.80 3.31	71.60* 2.48	25.60 4.32	25.40 6.18

Table VI-A: Changes in physiological parameters in response to hypoxia before and after BMW.
* Significant as compared to pre- and post-wounding hypoxia respectively; $p<0.05$; Mean +SE

	BEFORE WOUNDING		AFTER WOUNDING	
	NORMOXIA	HYPOXIA	NORMOXIA	HYPOXIA
MABP (mm Hg)	118.75 20.48	132.25 22.71	138.50 26.00	155.25 19.26
ICP (mm Hg)	13.00 1.78	14.00 1.08	60.00 11.19	66.50 19.25
CPP (mm Hg)	105.75 20.99	118.25 21.75	78.50 30.85	86.75 29.02
CVR	3.20 0.62	2.63 0.38	4.12 2.15	3.84 0.61
pH	7.39 0.04	7.40 0.03	7.30 0.06	7.33 0.07
PaCO2 (mm Hg)	31.22 2.06	29.52 1.27	33.10 0.89	31.85 1.65
PaO2 (mm Hg)	126.58 6.74	54.15* 3.35	126.50 2.02	53.22* 1.95
[H+] n mol/l	40.70	39.80	50.10	46.80
BLOOD GLUCOSE (mg/dl)	154.95 16.40	165.65 23.63	291.63 36.64	316.85 36.88
HEMATOCRIT (%)	30.75 4.21	33.00 4.64	31.25 3.71	34.00 4.51

Table VI-8: Changes in rCBF (ml/100g/min) in response to hypoxia before and after BMW.
* Significant as compared to pre- and post-wounding normoxia respectively; $p<0.05$; Mean ±SE.

	BEFORE WOUNDING		AFTER WOUNDING	
	NORMOXIA	HYPOXIA	NORMOXIA	HYPOXIA
FRONTAL CORTEX	33.25 5.41	44.75 8.67	25.25 2.06	23.50 10.41
PARIETAL CORTEX	34.75 2.66	43.25 3.82	21.75 1.25	22.25 8.06
TEMPORAL CORTEX	23.75 2.50	36.00* 2.35	17.50 3.93	24.50 5.72
OCCIPITAL CORTEX	41.75 5.39	51.25 7.28	20.50 2.72	22.75 5.57
WHITE MATTER	28.50 2.25	34.25* 3.75	17.25 3.68	19.00 5.07
CAUDATE NUCLEUS	52.25 6.05	66.75 9.45	29.75 10.40	29.00 11.67
HIPPOCAMPUS	24. 5 4.01	31.00* 2.45	15.75 2.06	21.25 7.16
THALAMUS	44.75 5.89	62.00* 8.80	28.00 4.30	32.25 10.63
HYPOTHALAMUS	22.50 5.55	33.50* 8.18	15.00 4.14	13.25 4.66
RETICULAR FORMATION	38.00 4.04	51.75 4.89	27.75 4.92	21.75 8.72
BRAINSTEM & MEDULLA	31.25 2.25	48.50* 6.40	25.00 4.88	21.25 6.94
CEREBELLUM-GRAY	40.50 4.21	62.25* 9.78	26.25 5.57	29.00 9.34
CEREBELLUM-WHITE	47.00 5.13	72.25* 10.56	29.00 6.24	36.75 7.49
PERIWOUND-GRAY	36.25 2.84	44.25 4.27	34.75 11.12	17.50 7.23
PERIWOUND-WHITE	33.25 3.01	38.50 * 4.48	27.25 10.27	19.50 9.92
WHOLE BRAIN	33.25 2.17	45.00* 4.43	22.50 3.48	23.25 6.34

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